The Synthesis of Highly Substituted Isoxazoles by Electrophilic Cyclization. An Efficient Synthesis of Valdecoxib.

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General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. The following starting materials were made according to literature procedures: 1,3-diphenylprop-2-yn-1-one,[1] 1-phenyl-2-butyn-1-one,[2] 4,4-dimethyl-1-phenylpent-1-yn-3-one, *N*-methyl-3-indolecarboxaldehyde,[3] 1-phenylnon-1-yn-3-one,[4] 2,2,6,6-tetramethylhept-4-yn-3-one,[5] 1-(furan-2-yl)-3-phenylprop-2-yn-1-one[6] and 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one. Compounds **1-4**, **7**, **8**, **21**, **22**, **25-28**, **37** and **38** have been reported in our previous communication.[7]

General procedure for the preparation of alkynones from acyl chlorides. To a 25 mL flask were added CuI (0.05 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and the terminal acetylene (2.5 mmol) was added to the stirred suspension, followed by immediate dropwise addition of benzoyl chloride (3.25 mmol, 1.3 equiv). If the acid chloride is a solid, it was added as a THF solution. The resulting mixture was allowed to stir at room temperature overnight, water (5 mL) was added, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel to afford the desired alkynone.

1-Phenylhept-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 381 mg (82%) of the product as a yellow oil with spectral properties identical to those previously reported.[8]

Ethyl 4-(3-oxo-3-phenylprop-1-ynyl)benzoate. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 570 mg (86%) of the product as a pale yellow solid: mp 54-56 ^{o}C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.42 (t, J = 7.2 Hz, 3H), 4.39-4.44 (q, J = 7.0 Hz, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.74-7.76 (d, J = 8.4 Hz, 2H), 8.1 (t, J = 8.2 Hz, 2H), 8.22-8.23 (d, J = 7.2 Hz, 2H); ^{13}C NMR δ 14.5,

61.7, 88.7, 91.5, 124.6, 128.9, 129.8 (2 carbons), 132.3, 133.0, 134.6, 136.8, 165.8, 177.9; HRMS Calcd for $C_{18}H_{14}O_3$: 278.0943. Found: 278.0947.

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded 470 mg (84%) of the product as a colorless solid: mp 121-122 ^{o}C (lit. 81-85 ^{o}C)[9] with spectral properties identical to those previously reported.[10]

1-Phenyl-3-(thiophen-2-yl)prop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 413 mg (78%) of the product as a yellow oil with spectral properties identical to those previously reported.[11]

3-Phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 413 mg (79%) of the product as a colorless solid: mp 75-77 ^{o}C (lit. 70-72 ^{o}C) with spectral properties identical to those previously reported.[12]

3-Phenyl-1-*o*-tolylprop-2-yn-1-one. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 440 mg (80%) of the product as a pale yellow liquid with spectral properties identical to those previously reported.[13]

4,4-Dimethyl-1-phenyl-2-pentyn-1-one. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 428 mg (92%) of the product as a pale yellow oil with spectral properties identical to those previously reported.[14]

1-(3,4,5-Trimethoxyphenyl)but-2-yn-1-one. A modified procedure was used. To a 25 mL flask were added CuI (0.05 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and 3,4,5-trimethoxybenzoyl chloride (3.25 mmol) in THF (5 mL) was added to the flask. The flask was flushed with propyne and a balloon of propyne gas was placed on the reaction flask. The resulting suspension was allowed to stir overnight. Purification by flash chromatography (4:1

hexanes/EtOAc) afforded 550 mg (94%) of the product as a pale yellow solid: mp 99-100 ^{o}C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.17 (s, 3H), 3.94 (s, 9H), 7.41 (s, 2H); ^{13}C NMR δ 4.6, 56.5, 61.2, 79.1, 92.4, 107.1, 132.2, 143.6, 153.2, 177.2; HRMS Calcd for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0895.

General procedure for the preparation of alkynones by the reaction of aldehydes with lithium acetylides, followed by oxidation with MnO_2. To a three-neck flask was added phenyl acetylene (11.2 mmol, 1.14 g) and anhydrous THF (7 mL). The stirred solution was cooled to 0 ºC and flushed with argon. To the stirred solution, *n*-BuLi (2.5 M in hexanes, 4.5 mL, 11.2 mmol) was added dropwise. The resulting mixture was allowed to stir for 30 min at 0 ºC. The aldehyde (9.3 mmol) in anhydrous THF (5 mL) was added dropwise and allowed to stir for 1 h at 0 ºC. The solution was quenched with a satd aq NH_4Cl solution and extracted with ether. The organic layers were combined, dried and concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL) and MnO_2 (27.9 mmol, 2.43 g) was added to the solution. The suspension was refluxed for 1 h, the solution was cooled and filtered through a pad of celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to afford the product. When the product was a solid, it was recrystallized from hexanes/EtOAc or hexanes/CH_2Cl_2 to afford spectroscopically pure product.

1-(2,6-Dimethoxyphenyl)-3-phenylprop-2-yn-1-one. The residue was purified by column chromatography on silica gel to afford 2.37 g (96%) of the product as an orange oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.83 (s, 6H), 6.57-6.59 (d, J = 8.4 Hz, 2H), 7.30-7.35 (m, 3H), 7.38-7.42 (m, 1H), 7.52-7.55 (td, J = 6.8, 1.6 Hz, 2H); ^{13}C NMR δ 56.1, 90.1, 90.5, 104.3, 119.0, 120.6, 128.6, 130.5, 132.2, 133.0, 158.1, 178.5; HRMS Calcd for $C_{17}H_{14}O_3$: 266.0943. Found 266.0947.

3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-one. The residue was purified by column chromatography on silica gel to afford 1.19 g (62%) of the product as a brown solid: mp 73-75 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.42-7.54 (m, 4H), 7.69-7.71 (dd, J = 8.2, 1.4

Hz, 2H), 8.42-8.45 (m, 1H), 8.84-8.86 (dd, J = 4.8, 1.6 Hz, 1H), 9.45 (t, J = 0.8 Hz, 1H); ^{13}C NMR δ 86.4, 94.8, 119.6, 123.7, 128.9, 131.4, 132.3, 133.4, 136.3, 151.5, 154.3, 176.5; HRMS Calcd for $C_{14}H_9NO$: 207.0684. Found: 207.0689.

1-[4(Dimethylamino)phenyl]-3-phenylprop-2-yn-1-one. The residue was purified by column chromatography on silica gel to afford 2.13 g (92%) of the product as a bright yellow solid: mp 155-156 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.09 (s, 6H), 6.67-6.69 (d, J = 9.2 Hz, 2H), 7.40-7.45 (m, 3H), 7.65-7.67 (m, 2H), 8.10-8.12 (dd, J = 7.2, 2.0 Hz, 2H); ^{13}C NMR δ 40.3, 87.6, 91.3, 110.8, 121.0, 125.7, 128.7. 130.3, 132.2, 133.0, 154.3, 176.2; HRMS Calcd for $C_{17}H_{15}NO$: 249.1154. Found: 249.1160.

1-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-one. The residue was purified by flash chromatography on silica gel (1:1 hexanes:$CHCl_3$) to afford 1.72 g (74%) of the product as a yellow oil with spectral properties identical to those previously reported.[15]

General procedure for preparation of the *O*-methyl oximes. The alkynone (3.5 mmol), methoxylamine hydrochloride (7.0 mmol, 579 mg), Na_2SO_4 (7.0 mmol, 994 mg) and pyridine (1 mL) in methanol (10 mL) were stirred at room temperature. The addition of the co-solvent benzene was used in cases where the ynone showed poor solubility in methanol. In some cases the reaction required refluxing conditions to go to completion. The reaction was monitored by TLC until the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine, dried and evaporated. The residue was then purified by column chromatography on silica gel, unless otherwise stated, to afford the desired *O*-methyl oxime.

(*Z*)-1-Phenylhept-2-yn-1-one *O*-methyl oxime (5). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 617 mg (82%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.93-0.98 (t, J = 7.3 Hz, 3H), 1.46-1.56 (m, 2H), 1.63-1.68 (m, 2H), 2.52-2.57 (t, J = 8.2 Hz, 2H), 4.08 (s, 3H), 7.35-7.37 (m, 3H),

7.82-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.7, 22.3, 30.6, 71.7, 104.2, 126.7, 128.5, 129.7, 134.1, 140.5; HRMS Calcd for $C_{14}H_{17}NO$: 215.1310. Found: 215.1314.

(*Z*)-Ethyl 4-(3-oxo-3-phenylprop-1-ynyl)benzoate *O*-methyl oxime (9).
Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 904 mg (82%) of the product as a colorless oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.15 (s, 21H), 4.07 (s, 3H), 7.34-7.37 (m, 3H), 7.84-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.4, 18.9, 63.2, 96.1, 105.6, 126.6, 128.6, 129.7, 133.8, 140.1; HRMS Calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1212.

(*Z*)-3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (11).
Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 677 mg (73%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.83 (s, 3H), 4.13 (s, 3H), 6.88-6.91 (d, J = 8.9 Hz, 2H), 7.38-7.40 (m, 3H), 7.54-7.57 (d, J = 8.9 Hz, 2H) 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 63.3, 78.8, 101.9, 114.0, 114.3, 126.7, 128.6, 129.8, 134.0, 134.1, 140.4, 160.9; HRMS Calcd for $C_{17}H_{15}NO_2$: 265.1103. Found: 265.1107.

(*Z*)-1-Phenyl-3-(thiophen-2-yl)prop-2-yn-1-one *O*-methyl oxime (13).
Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 523 mg (62%) of the product as a pale yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.13 (s, 3H), 7.02-7.05 (m, 1H), 7.38-7.41 (m, 5H), 7.86-7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 63.4, 83.7, 94.7, 121.7, 126.7, 127.6, 128.7, 129.6, 130.0, 133.6, 134.3, 140.0; HRMS Calcd for $C_{14}H_{11}NOS$: 241.0561. Found: 241.0566.

(*Z*)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (15).
Purification by flash chromatography (6:1 hexanes/$CHCl_3$) afforded 621 mg (69%) of the product as a colorless solid: mp 52-54 ^{o}C: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.13 (s, 3H), 7.34-7.41 (m, 5H), 7.59-7.62 (m, 2H), 7.83-7.86 (dt, J = 8.8, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 63.4, 79.2, 101.7, 121.7, 127.9, 128.7, 128.8, 129.9, 132.2, 132.3, 135.8, 139; HRMS Calcd for $C_{16}H_{12}ClNO$: 269.0607. Found: 269.0611.

(*Z*)-3-Phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-one *O*-methyl oxime (17). Purification by flash chromatography (3:1 hexanes/ $CHCl_3$) afforded 530 mg (50%) of the product as a tan solid: mp 41-43 ^oC; ^1H NMR ($CDCl_3$ 400 MHz) δ 4.17 (s, 3H), 7.36-7.43 (m, 3H), 7.61-7.66 (m, 4H), 8.02-8.04 (dd, J = 8.0, 0.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 63.69, 79.10, 102.20, 121.65, 125.53, 125.57, 125.61, 125.65, 125.95, 126.95, 126.96, 126.99, 128.75, 128.76, 128.77, 130.03, 132.39, 132.41, 132.42, 132.43, 137.15, 138.92 (extra peaks due to C-F coupling); HRMS Calcd for $C_{17}H_{12}F_3NO$: 303.0871. Found: 303.0875.

(*Z*)-1-[4(Dimethylamino)phenyl]-3-phenylprop-2-yn-1-one *O*-methyl oxime (19). Purification by flash chromatography ($CHCl_3$) afforded 710 mg (73%) of the product as a yellow solid: mp 81-83 ^oC: ^1H NMR ($CDCl_3$ 400 MHz) δ 2.99 (s, 6H), 4.10 (s, 3H), 6.69-6.71 (m, 2H), 7.35-7.39 (m, 3H), 7.60-7.62 (m, 2H), 7.76-7.80 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 40.6, 63.0, 80.2, 100.5, 111.9, 122.3, 127.8, 128.6, 129.5, 132.4, 140.3, 151.6; HRMS Calcd for $C_{18}H_{18}N_2O$: 278.1419. Found: 278.1424.

(*Z*)-4-Phenylbut-3-yn-2-one *O*-methyl oxime (23). Purification by flash chromatography on basic alumina (hexanes) afforded 291 mg (48%) of the product as a colorless liquid: ^1H NMR ($CDCl_3$ 300 MHz) δ 2.13 (s, 3H), 3.97 (s, 3H), 7.34-7.36 (m, 3H), 7.51-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 62.5, 81.2, 99.3, 121.9, 128.6, 129.6, 132.3, 137.8; HRMS Calcd for $C_{11}H_{11}NO$: 173.0841. Found: 173.0845.

(*Z*)-3-Phenyl-1-*o*-tolylprop-2-yn-1-one *O*-methyl oxime (29). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 488 mg (56%) of the product as a yellow oil: ^1H NMR ($CDCl_3$ 400 MHz) δ 2.54 (s, 3H), 4.12 (s, 3H), 7.22-7.35 (m, 6H), 7.52-7.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.1, 63.3, 80.9, 101.5, 122.0, 126.2, 128.7, 129.4, 129.7, 129.8, 131.3, 132.3, 133.6, 137.1, 141.1; HRMS Calcd for $C_{17}H_{15}NO$: 249.1154. Found: 249.1158.

(*Z*)-1-(2,6-Dimethoxyphenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (31). Purification by flash chromatography ($CHCl_3$) afforded 630 mg (61%) of the product as a yellow solid: mp 144-146 ^oC: ^1H NMR ($CDCl_3$ 400 MHz) δ 3.83 (s, 6H), 4.11 (s, 3H), 6.58-6.60 (d, *J* = 8.4 Hz, 2H), 7.27-7.33 (m, 4H), 7.49-7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.4, 63.1, 81.4, 98.6, 104.4, 112.2, 122.4, 128.5, 129.3, 131.0, 132.4, 135.0, 159.0; HRMS Calcd for $C_{18}H_{17}NO_3$: 295.1208. Found: 295.1212.

(*Z*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (33). Purification by flash chromatography (1:1 hexanes/$CHCl_3$) afforded 322 mg (53%) of the product as a pale yellow oil: ^1H NMR ($CDCl_3$ 400 MHz) δ 4.11 (s, 3H), 5.99 (s, 2H), 6.82-6.84 (d, *J* = 8.0, 0.8 Hz, 1H), 7.36-7.45 (m, 5H), 7.59-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 63.1, 79.6, 101.1, 101.7, 106.4, 108.3, 121.8, 121.9, 128.1, 128.8, 132.4, 139.6, 148.1, 149.3; HRMS Calcd for $C_{17}H_{13}INO_3$: 279.0895. Found: 279.0900.

(*Z*)-1-(Furan-2-yl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (35). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 575 mg (73%) of the product as a pale yellow oil: ^1H NMR ($CDCl_3$ 400 MHz) δ 4.14 (s, 3H), 6.47-6.48 (m, 1H), 6.82-6.83 (d, *J* = 3.8 Hz, 1H), 7.34-7.40 (m, 3H), 7.49 (t, *J* = 0.8 Hz, 1H), 7.58-7.6 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 63.6, 78.2, 99.6, 111.8, 112.7, 121.6, 128.7, 130.0, 132.2, 132.4, 144.4, 148.3; HRMS Calcd for $C_{14}H_{11}NO_2$: 225.0789. Found: 225.0793.

(*Z*)-3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-one *O*-methyl oxime (39) Purification by flash chromatography (2:1 hexanes/EtOAc) afforded 471 mg (57%) of the product as an orange oil: ^1H NMR ($CDCl_3$ 300 MHz) δ 4.16 (s, 3H), 7.29-7.40 (m, 4H), 7.60-7.63 (m, 2H) 8.16-8.20 (m, 1H), 8.62-8.64 (dd, *J* = 4.8, 1.6 Hz, 1H), 9.14-9.15 (dd, *J* = 2.3, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 63.6, 78.7, 102.3, 121.6, 123.4, 128.7, 129.7, 130.1, 132.4, 133.6, 137.7, 148.3, 150.7; HRMS Calcd for $C_{15}H_{12}N_2O$: 236.0950. Found: 236.0953.

(*Z*)-2,2,6,6-Tetramethylhept-4-yn-3-one *O*-methyl oxime (41). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded 566 mg (83%) of the product as a

pale yellow oil: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.17 (s, 9H), 1.31 (s, 9H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 28.35, 28.36, 30.9, 37.1, 62.3, 69.9, 110.9, 149.7; HRMS Calcd for $C_{12}H_{21}NO$: 195.1623. Found: 195.1626.

(*Z*)-1-(3,4,5-Trimethoxyphenyl)but-2-yn-1-one *O*-methyl oxime (43). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 838 mg (91%) of the product as a pale yellow solid: mp 99-100 ^{o}C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.21 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 4.09 (s, 3H), 7.09 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 5.1, 56.3, 61.0, 63.1, 70.8, 99.5, 103.9, 129.4, 139.6, 140.0, 153.1; HRMS Calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1162.

General procedure for iodocyclization using ICl. To a stirred solution of the appropriate *O*-methyl oxime (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added ICl (1M in CH_2Cl_2, 1.2 equiv) dropwise and the solution was allowed to stir at room temperature. The reaction was monitored by TLC to establish completion. The excess ICl was removed by washing with a satd aq soln of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/EtOAc or hexanes/$CHCl_3$ as the eluent.

5-Butyl-4-iodo-3-phenylisoxazole (6). The product was obtained as a pale yellow oil; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 0.97 (t, J = 7.3 Hz, 3H), 1.37-1.49 (m, 2H), 1.72-1.80 (m, 2H), 2.88 (t, J = 7.6 Hz, 2H), 7.47-7.49 (m, 3H), 7.76-7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 27.1, 29.5, 57.5, 128.7 (2 carbons), 129.0, 130.1, 162.9, 175.0; HRMS Calcd for $C_{13}H_{14}INO$: 327.0120. Found: 327.0126.

Ethyl 4-(4-iodo-3-phenylisoxazol-5-yl)benzoate (10). The product was obtained as a colorless solid: mp 151-153 ºC; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.43 (t, J = 7.2 Hz, 3H), 4.39-4.46 (q, J = 7.1 Hz, 2H), 7.51-7.54 (m, 3H) 7.76-7.80 (m, 2H), 8.16-8.22 (m,

4H); ^{13}C NMR ($CDCl_3$) δ 14.6, 57.8, 61.6, 127.8, 128.7, 128.8, 129.2, 130.1, 130.4, 131.2, 132.4, 165.2, 166.0, 168.0; HRMS Calcd for $C_{18}H_{14}INO_3$: 419.0019. Found: 419.0026.

4-Iodo-5-(4-methoxyphenyl)-3-phenylisoxazole (12). The product was obtained as a colorless solid: mp 153-155 ºC; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.88 (s, 3H), 7.02-7.05 (m, 2H), 7.47-7.52 (m, 3H), 7.76-7.80 (m, 2H), 8.03-8.06 (dd, *J* = 9.1, 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.9, 55.7, 114.4, 120.0, 128.7, 129.1, 129.2, 129.6, 130.2, 161.6, 164.9, 169.1; HRMS Calcd for $C_{16}H_{12}INO_2$: 376.9913. Found: 376.9918.

4-Iodo-3-phenyl-5-(thiophen-2-yl)isoxazole (14). The product was obtained as a yellow solid: mp 118-120 ºC; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.20-7.23 (dt, *J* = 3.8, 1.2 Hz, 1H), 7.49-7.54 (m, 3H), 7.56-7.81 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.76-7.81 (m, 2H), 7.98-8.00 (dd, *J* = 3.8, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 54.9, 55.7, 114.4, 120.0, 128.7, 129.1, 129.2, 129.6, 130.2, 161.6, 164.9, 169.1; HRMS Calcd for $C_{13}H_8INOS$: 352.9371. Found: 352.9376.

3-(4-Chlorophenyl)-4-iodo-5-phenylisoxazole (16). The product was obtained as a colorless solid: mp 165-167 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.48-7.53 (m, 5H), 7.72-7.76 (td, *J* = 8.8, 2.2 Hz, 2H), 8.04-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0, 127.3, 127.4, 128.0, 129.0, 129.1, 130.5, 131.1, 136.6, 164.0; HRMS Calcd for $C_{15}H_9ClINO$: 380.9417. Found: 380.9425.

4-Iodo-5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazole (18). The product was obtained as a pale yellow solid: mp 174-175 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.52-7.55 (m, 3H), 7.77-7.79 (d, *J* = 8.0 Hz, 2H), 7.92-7.94 (d, *J* = 8.4 Hz, 2H), 8.06-8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.72, 125.74, 125.78, 125.81, 125.85, 127.18, 128.01, 128.02, 128.03, 129.05, 129.06, 129.65, 129.67, 131.19, 163.87, 169.73 (extra peaks due to C-F coupling); HRMS Calcd for $C_{16}H_9F_3INO$: 416.9681. Found: 414.9686.

4-Iodo-3-[4(dimethylamino)phenyl]-5-phenylisoxazole (20). The product was obtained as a pale yellow solid: mp 148-149 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.04 (s, 6H), 6.80-6.82 (d, *J* = 8.8 Hz, 2H), 7.49-7.53 (m, 3H), 7.72-7.74 (td, *J* = 7.0, 2.1 Hz, 2H), 8.05-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 40.5, 56.6, 111.9, 127.7, 128.0, 128.8, 128.9, 130.0, 130.7, 151.5, 164.6, 168.7; HRMS for $C_{17}H_{15}IN_2O$: 390.0229. Found: 390.0234.

4-Iodo-3-methyl-5-phenylisoxazole (24). The product was isolated as a pale yellow oily solid: mp 31-34 ºC; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.35 (s, 3H), 7.48-7.50 (m, 3H), 8.01-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 58.0, 127.4, 127.5, 128.9, 130.7, 163.2, 167.5; HRMS for $C_{10}H_8INO$: 284.9651. Found: 284.9654.

4-Iodo-5-phenyl-3-*o*-tolylisoxazole (30). The product was obtained as a pale yellow solid: mp 84-86 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.31 (s, 3H), 7.28-7.34 (m, 4H), 7.38-7.41 (m, 1H), 7.50-7.54 (m, 3H), 8.12-8.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.3, 58.8, 126.0, 127.4, 127.7, 128.7, 129.0, 130.2, 130.4, 130.7, 131.0, 137.7, 166.9, 168.2; HRMS Calcd for $C_{16}H_{12}INO$: 360.9964. Found: 360.9968.

3-(2,6-Dimethoxyphenyl)-4-iodo-5-phenylisoxazole (32). The product was obtained as a yellow solid: mp 141-143 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.78 (s, 6H), 6.65-6.67 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.47-7.52 (m, 2H), 8.12-8.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.3, 60.7, 104.7, 106.7, 127.6, 127.8, 128.9, 130.6, 132.1, 159.1, 162.6, 167.5; HRMS Calcd for $C_{17}H_{14}INO_3$: 407.0019. Found: 407.0026.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-iodo-5-phenylisoxazole (34). The product was obtained as a colorless solid: mp 126-128 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.05 (s, 2H), 6.93-6.95 (dd *J* = 8.0, 0.4 Hz, 1H), 7.25-7.26 (m, 1H), 7.30-7.33 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.51-7.54 (m, 3H), 8.04-8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.4, 101.8, 108.7, 109.5, 122.5, 123.6, 127.5, 128.0, 129.0, 130.9, 148.0, 149.4, 164.5, 169.2; HRMS Calcd for $C_{16}H_{10}INO_3$: 390.9705. Found: 390.9712.

3-(Furan-2-yl)-4-iodo-5-phenylisoxazole (36). The product was obtained as an orange solid: mp 50-53 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.37-6.38 (d, *J* = 3.6 Hz, 1H), 7.34-7.35 (d, *J* = 3.6 Hz, 1H), 7.52-7.54 (m, 4H), 8.02-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.3, 108.4, 114.9, 126.9, 128.1, 129.0, 131.2, 139.5, 142.9, 155.7, 169.6; HRMS Calcd for $C_{13}H_8INO_2$: 336.9600. Found: 3363.9606.

3-(4-Iodo-5-phenylisoxazol-3-yl)pyridine (40). The product was obtained as a pale yellow solid: mp 144-146 ºC; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.44-7.49 (m, 1H), 7.54-7.56 (m, 3H), 8.06-8.15 (m, 3H), 8.76-8.77 (dd, *J* = 4.9, 1.6 Hz, 1H), 9.07 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 123.5, 125.3, 127.1, 128.0, 129.1, 131.2, 136.6, 149.8, 151.3, 162.7, 169.7; HRMS Calcd for $C_{14}H_9IN_2O$: 347.9760. Found: 347.9765.

3,5-Di-*tert*-butyl-4-iodoisoxazole (42). The product was obtained as a colorless solid: mp 106-108 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.47 (s, 9H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 28.4, 28.5, 33.8, 34.6, 50.6, 169.4, 177.6; HRMS Calcd for $C_{11}H_{18}INO$: 307.0433. Found: 307.0437.

4-Iodo-5-methyl-3-(3,4,5-trimethoxyphenyl)isoxazole (44). The product was obtained as a colorless solid: mp 148-150 ºC; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.56 (s, 3H), 3.91 (s, 3H), 3.93 (s, 6H), 7.06 (s, 2H) ; ^{13}C NMR ($CDCl_3$) δ 13.2, 56.4, 57.9, 61.1, 105.8, 124.0, 139.6, 153.4, 162.4, 171.7; HRMS Calcd for $C_{13}H_{14}INO_4$: 374.9968. Found: 374.9971.

Procedure for the Suzuki-Miyaura cross-coupling to form 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (valdecoxib) (46). To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.25 mmol, 71 mg), benzenesulfonamide-4-boronic acid pinacol ester (0.35 mmol, 99 mg), $KHCO_3$ (0.35 mmol, 35 mg) and $PdCl_2$ (0.0125 mmol, 2.2 mg) in 4:1 DMF:H_2O (2.5 mL). The solution was stirred for 5 min at room temperature and flushed with argon and then heated to 80 ^{o}C for 2 h. The product was concentrated under reduced pressure and isolated by column chromatography on silica gel (2:3 hexanes/EtOAc) to afford 4-(5-methyl-3-phenyl-4-

isoxazolyl)benzenesulfonamide (valdecoxib) **(46)** as a colorless solid: mp 160-162 °C (lit.[16] 155-157 °C, lit.[17] 172-173 °C) with spectral properties identical to those previously reported.[16,17]

Procedure for the palladium-catalyzed carbonylative esterification to form methyl 3,5-diphenylisoxazole-4-carboxylate (47). To a 4-dram vial was added 4-iodo-3,5-diphenylisoxazole (0.44 mmol, 152 mg), $Pd(OAc)_2$ (0.0132 mmol, 2.8 mg), DPPF (0.028 mmol, 14.8 mg) in 4:1 DMF:H_2O (1.25 mL). The reaction mixture was evacuated and back-filled with carbon monoxide three times. A balloon of carbon monoxide was attached to the vial, which was heated to 55 °C for 18 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 10:1 hexanes/EtOAc to afford the compound as a colorless solid: mp 94-96 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.72 (s, 3H), 7.48-7.54 (m, 6H), 7.65-7.67 (m, 2H), 7.67-7.93 (dd, J = 7.8, 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.2, 108.2, 127.0, 128.5 (2 peaks), 128.7, 128.8, 128.9, 129.1, 130.1, 131.5, 163.1, 163.2, 172.7; HRMS Calcd for $C_{17}H_{13}NO_3$: 279.0895. Found: 279.0899.

Procedure for the palladium-catalyzed carbonylative amidation to form *N*-phenethyl-5-methyl-3-phenylisoxazole-4-carboxamide (48). A modified literature procedure was used.[18] To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.17 mmol, 48 mg), $PdCl_2(PPh_3)_2$ (0.0085 mmol, 6 mg), 2-phenethyl amine (0.25 mL) in DMF (1 mL). The reaction mixture was evacuated and back-filled with carbon monoxide three times. A balloon of carbon monoxide was placed on the vial, which was heated to 80 °C for 18 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 4:1 hexanes/EtOAc to afford the compound as a colorless solid: mp 145-146 °C; ^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.51 (s, 3H), 2.71 (t, J = 6.8 Hz, 2H), 3.51-3.56 (q, J = 6.8 Hz, 2H), 5.41 (br s, 1H), 6.96-6.98 (dd, J = 7.2, 1.6 Hz, 2H), 7.20-7.26 (m, 3H), 7.39-7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ

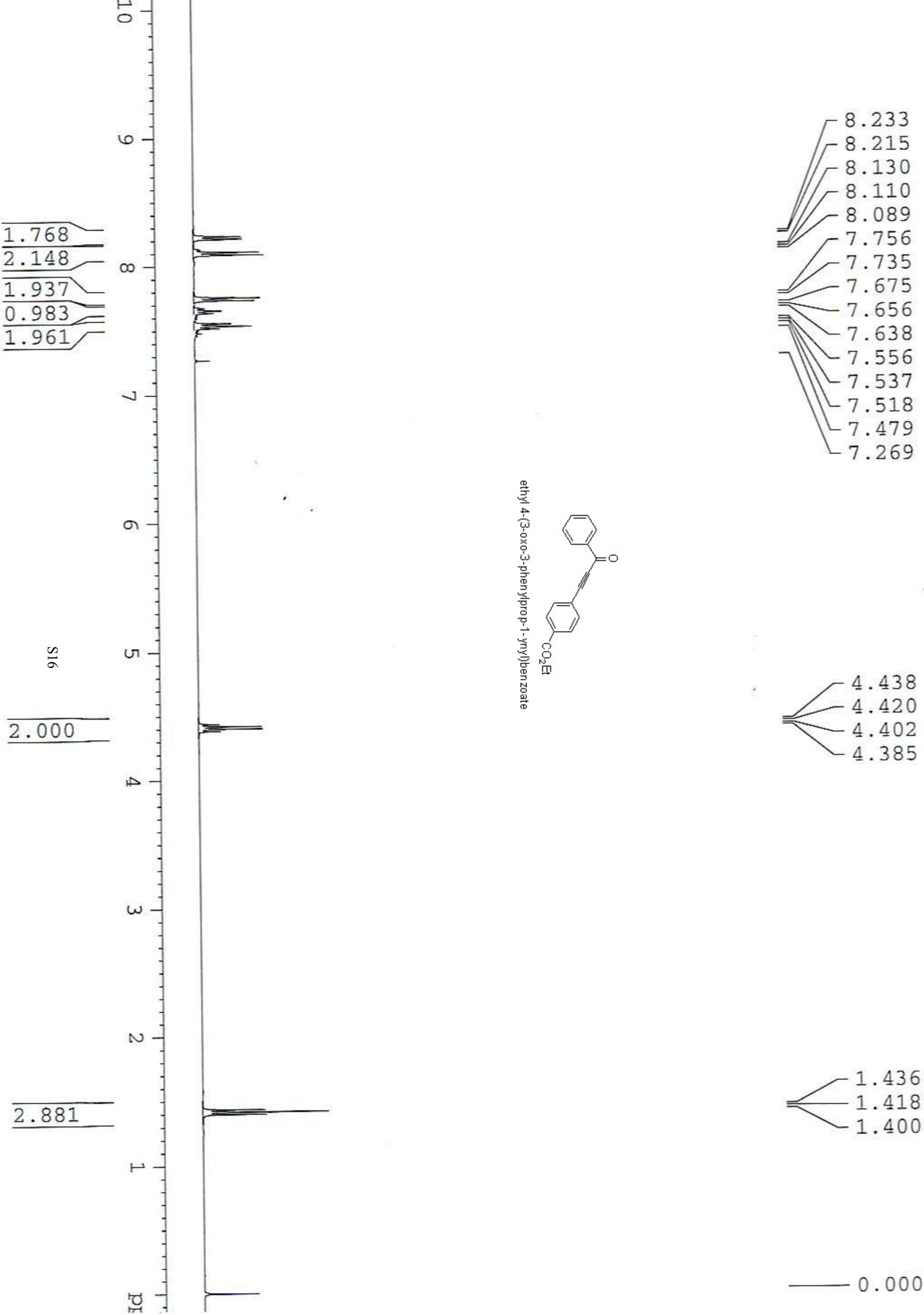
13.2, 35.2, 40.7, 111.2, 126.8, 128.3, 128.7, 128.9, 129.1, 129.3, 130.6, 138.5, 160.3, 161.7, 174.3; HRMS Calcd for $C_{19}H_{18}N_2O_2$: 306.1368. Found: 306.1374.

Procedure for the Sonogashira coupling to form 5-methyl-3-phenyl-4-(phenylethynyl)isoxazole (49). To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.5 mmol, 142 mg), phenyl acetylene (0.6 mmol, 61.2 mg), $PdCl_2(PPh_3)_2$ (0.005 mmol, 3.5 mg), CuI (0.01 mmol, 1.9 mg), DMF (1.5 mL) and Et_2NH (1.85 mL). The solution was stirred for 5 minutes at room temperature and flushed with argon and then heated to 50 ^oC for 6 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 10:1 hexanes/EtOAc to afford the compound as a brown solid: mp 98-100 ^oC; ^1H NMR ($CDCl_3$ 400 MHz) δ 2.58 (s, 3H), 7.35 (t, J = 4.2 Hz, 3H), 7.46-7.51 (m, 5 H), 8.09-8.12 (dd, J = 7.2, 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.3, 78.4, 95.1, 99.5, 122.9, 127.7, 128.6, 128.7, 128.8, 130.3, 131.6, 161.3, 173.1; HRMS Calcd for $C_{18}H_{13}NO$: 259.0997. Found: 259.1001.

Procedure for the Heck coupling to form (*E*)-3-(5-methyl-3-phenylisoxazol-4-yl)-1-morpholinoprop-2-en-1-one (50). To a 4-dram vial was added 4-iodo-5-methyl-3-phenylisoxazole (0.25 mmol, 71 mg), *N*-acryloylmorpholine (1.0 mmol, 141 mg), $PdOAc_2$ (0.0132 mmol, 2.8 mg), TBAC (0.25 mmol, 69 mg), Na_2CO_3 (0.625 mmol, 66 mg) and DMF (1 mL), which was then heated to 85 ^oC for 24 h. The solution was allowed to cool and was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried and concentrated. The residue was purified by column chromatography using 1:1 hexanes/EtOAc to afford the compound as a yellow oil; ^1H NMR ($CDCl_3$ 400 MHz) δ 2.59 (s, 3H), 3.27 (br s, 2H), 3.60 (br s, 2H), 3.68 (br s, 4H), 6.28-6.33 (d, J = 15.3 Hz, 1H), 7.46-7.51 (m, 4H), 7.53-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.3, 42.5, 46.0, 66.8, 111.7, 118.5, 128.9, 129.0, 129.2, 130.0, 130.8, 161.8, 165.1, 169.3; HRMS Calcd for $C_{17}H_{18}N_2O_3$: 298.1317. Found: 298.1321.

References

1. Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.
2. Herrero, M. T.; Tellitu, I.; Domínguez, E.; Hernández, S.; Moreno, I., San Martín, R. *Tetrahedron* **2002**, *58*, 8581.
3. Moody, C. J.; Ward, J. G. *J. Chem. Soc., Perkin. Trans. I*. **1984**, 2903.
4. Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.
5. Van den Hoven, B. G.; El Ali, B.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4131.
6. Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615.
7. Waldo, J. P.; Larock, R. C. *Org. Lett*. **2005**, *23*, 5203.
8. Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. C*hem. Commun.* **2005**, 1037.
9. Fetter, J.; Nagy, I.; Giang, L. T.; Kajtar-Peredy, M.; Rockenbauer, A.; Korecz, L.; Czira, G. *J. Chem. Soc., Perkin Trans*. 1 **2001**, 1131.
10. Kang, S.; Ryu, H.; Hong, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 736.
11. Negishi, E.; Qian, M.; Zeng, F.; Nastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.
12. Rao, P. N. P.; Uddin, M. J.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 3972.
13. Fukuyama, T.; Yamaura, R.; Ryu, I. *Can. J. Chem.* **2005**, *83*, 711.
14. Mahomed Ahmed, M. S.; Mori, A. *Org. Lett.* **2003**, *5*, 3057.
15. Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601.
16. J. J. Talley (G. D. Searle & Company), U.S. Patent 5,859,257, 1999; *Chem. Abstr.* **1999**, *130*, 110269.
17. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem*. **2000**, *43*, 775.
18. Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.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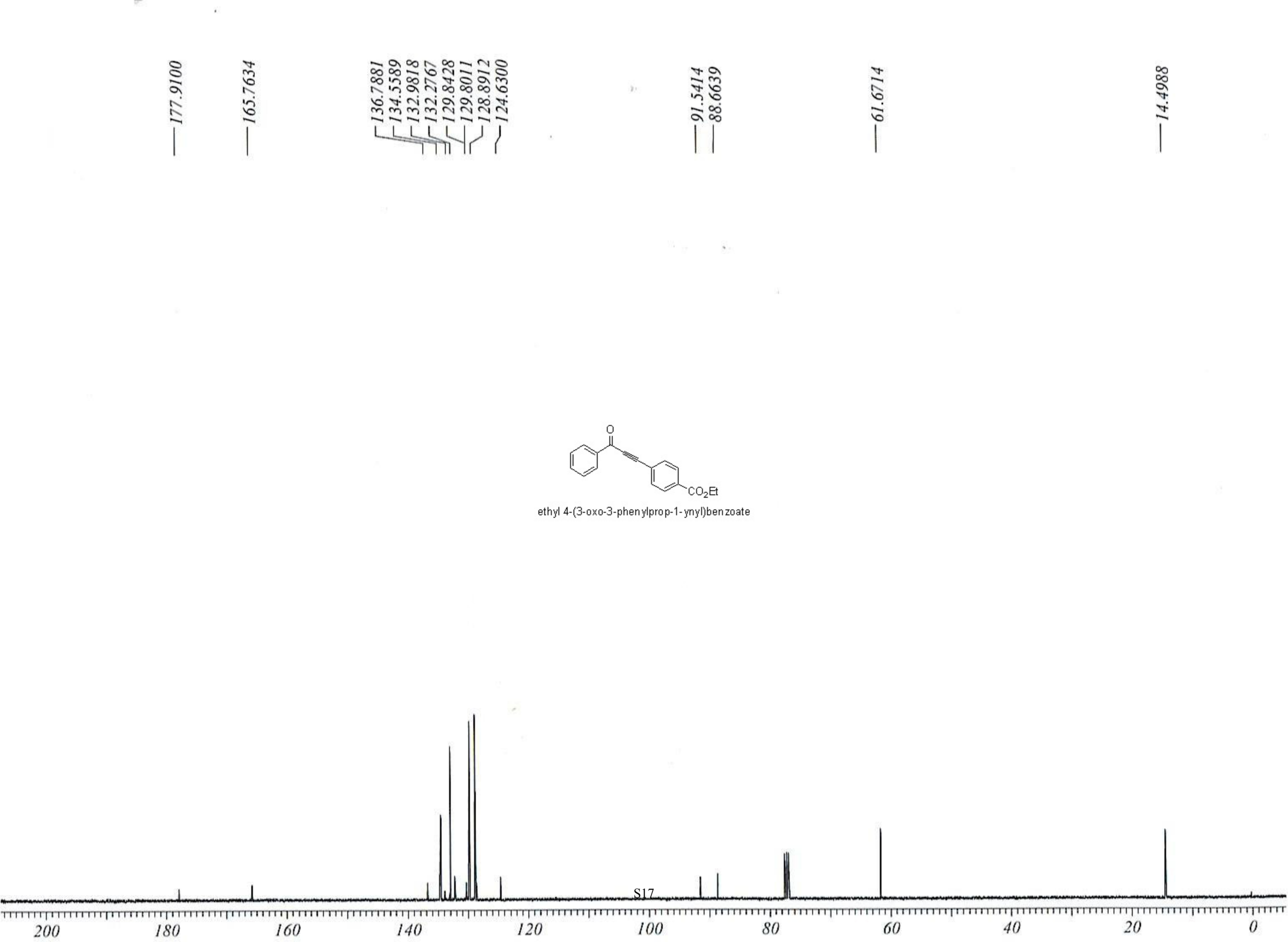
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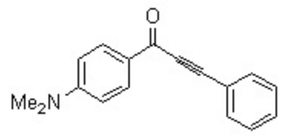

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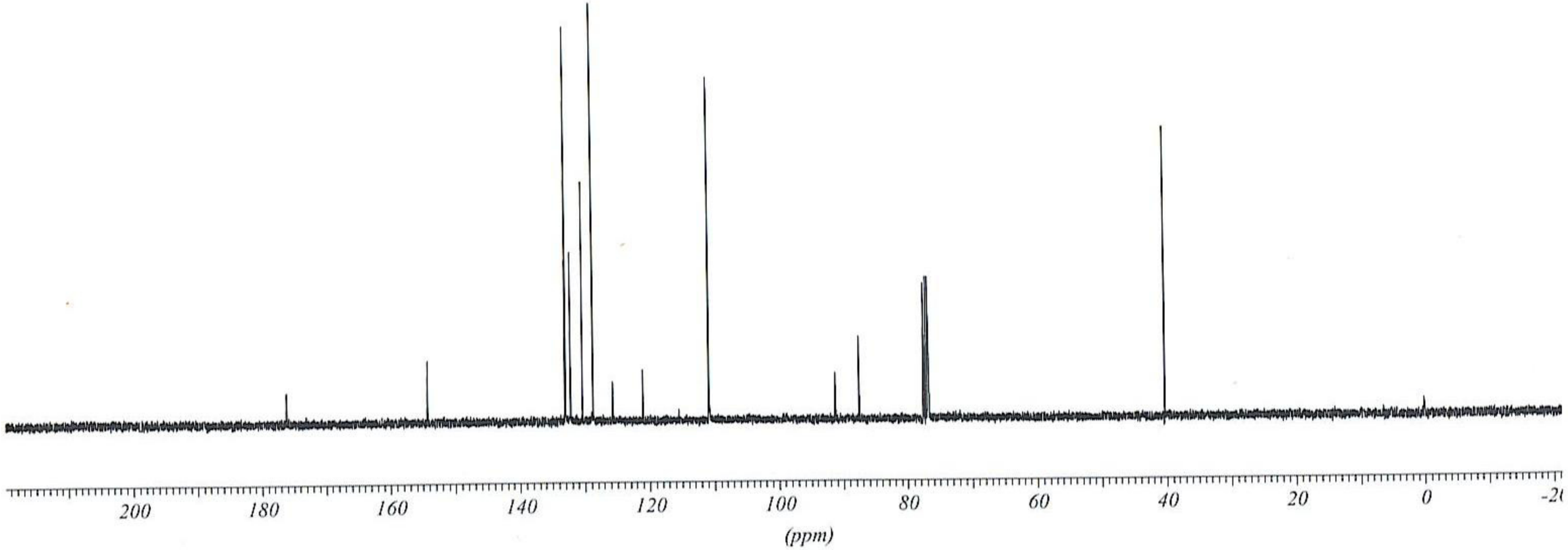

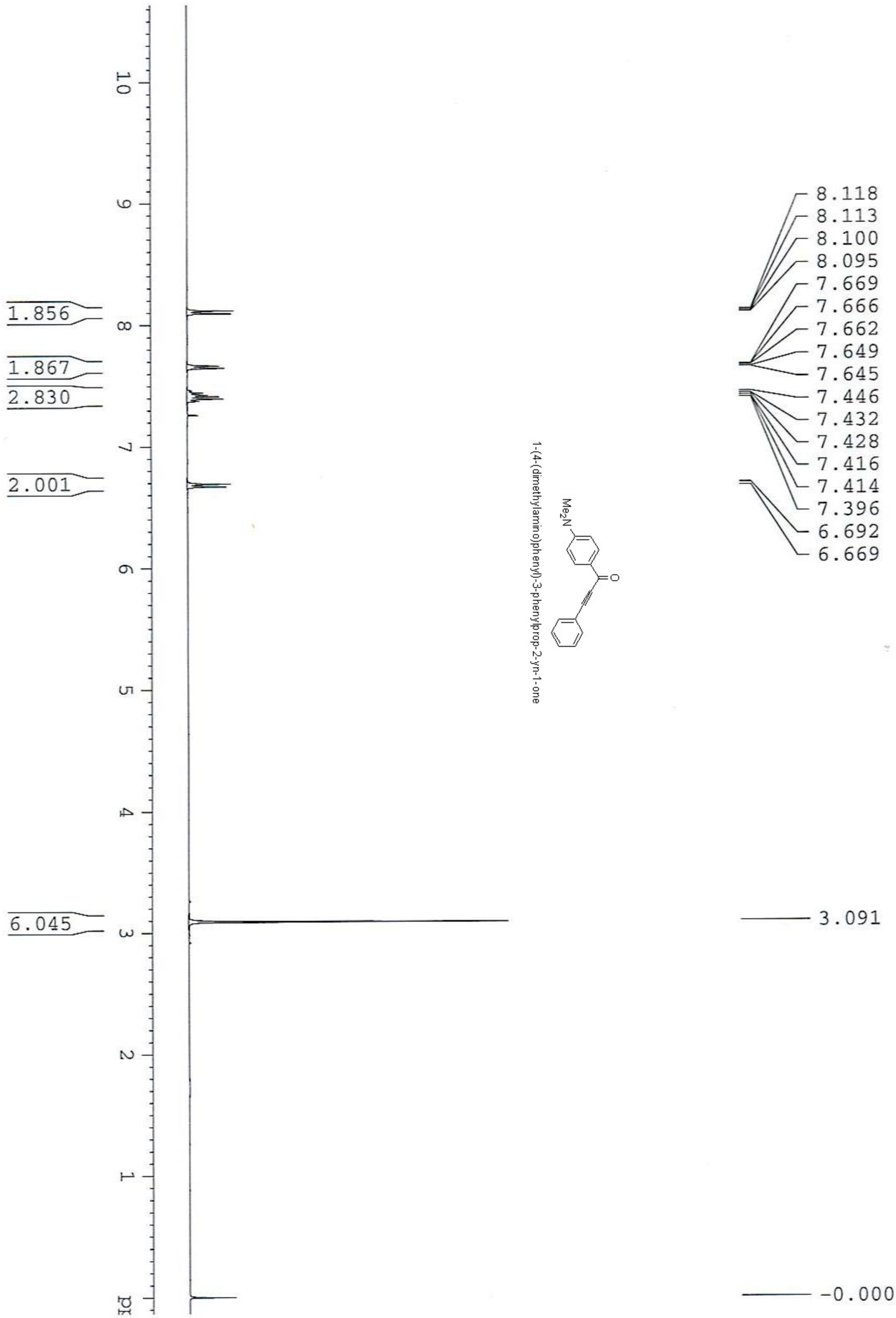
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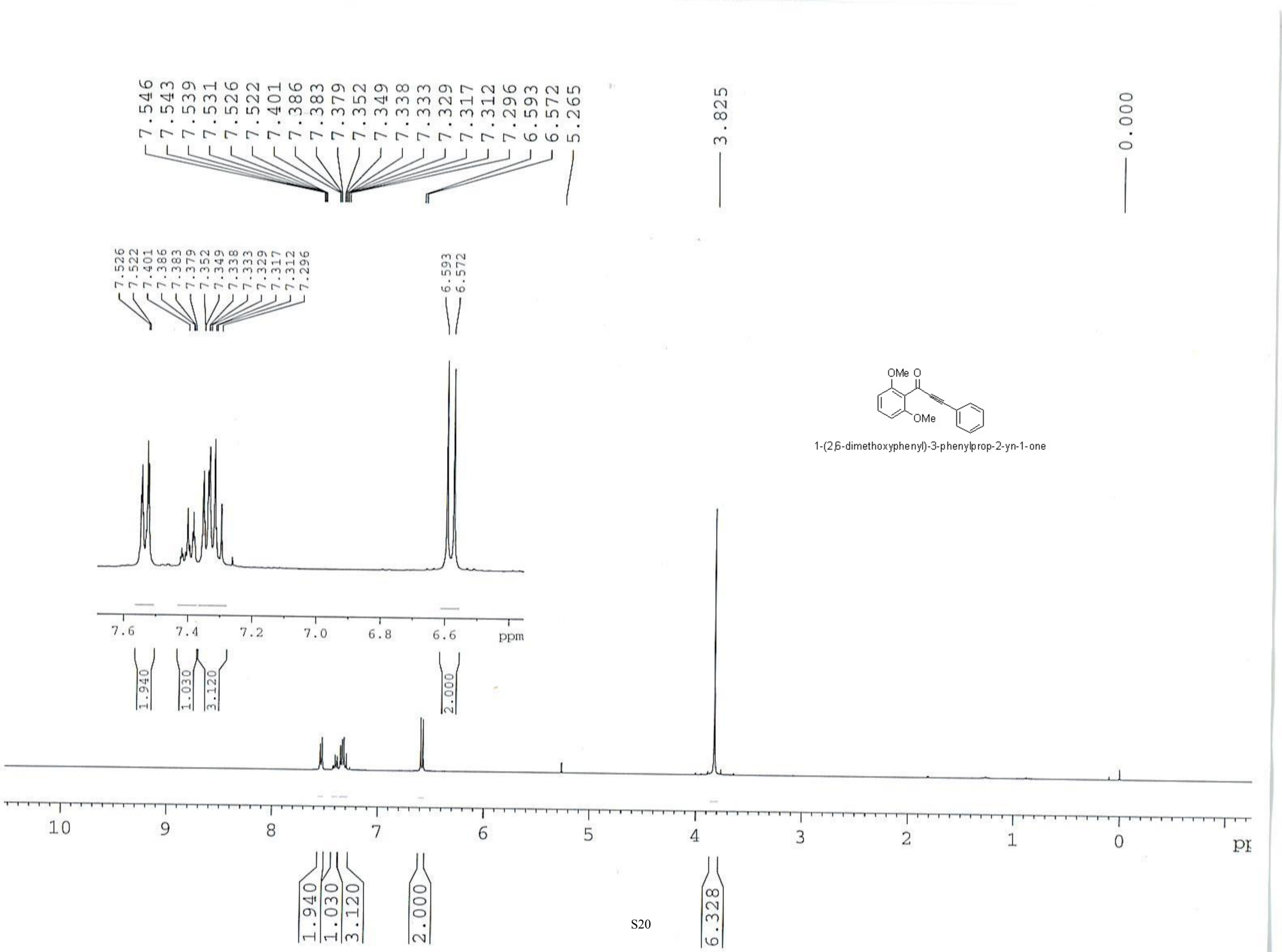
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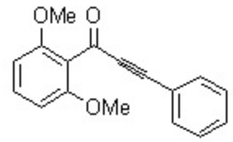

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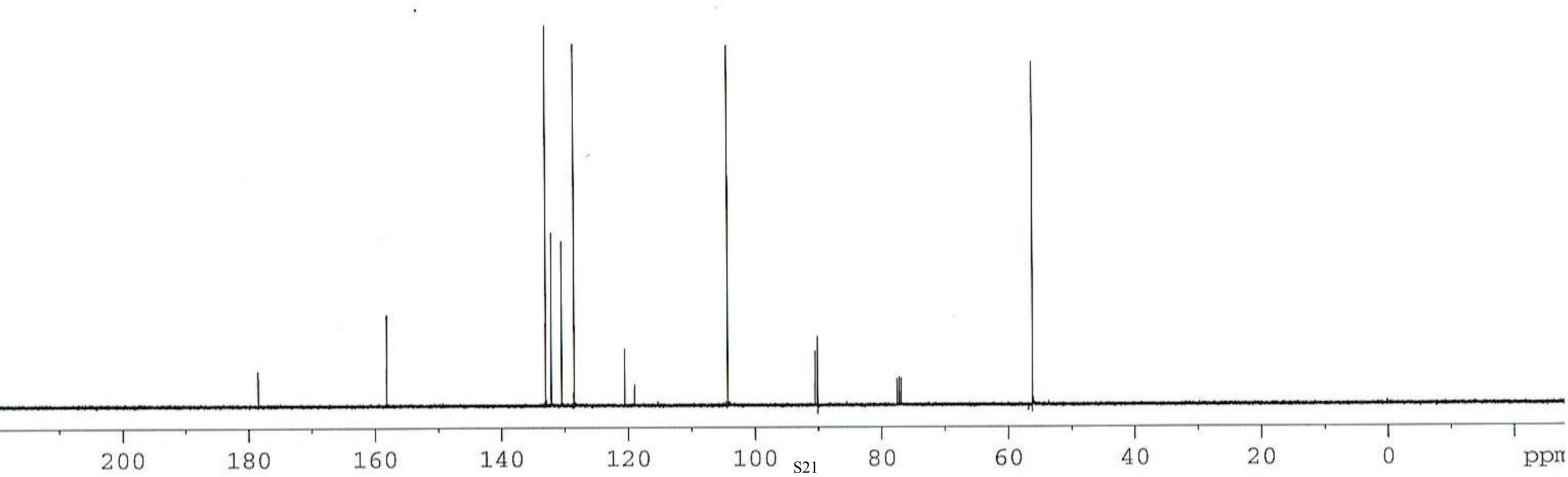

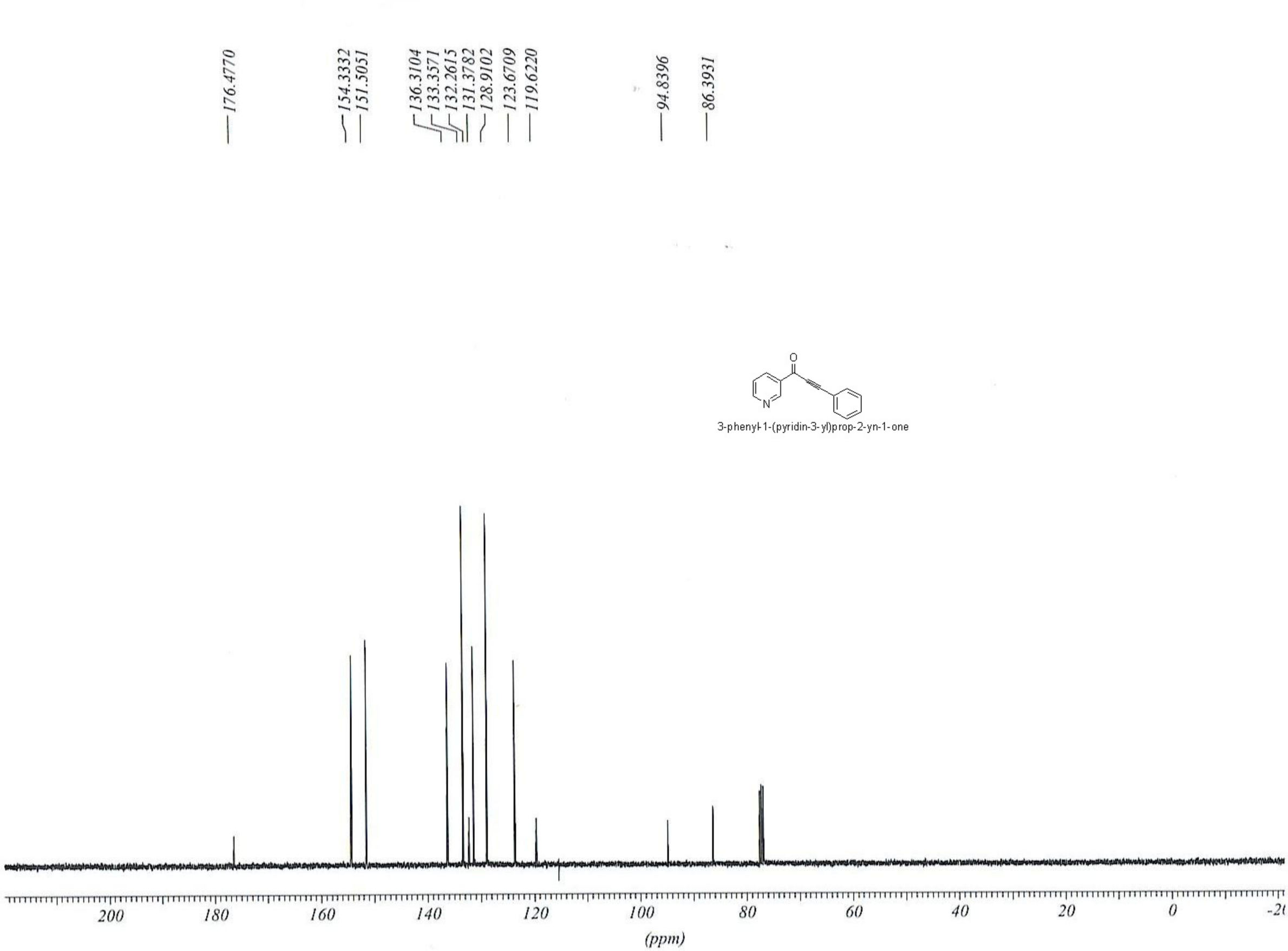
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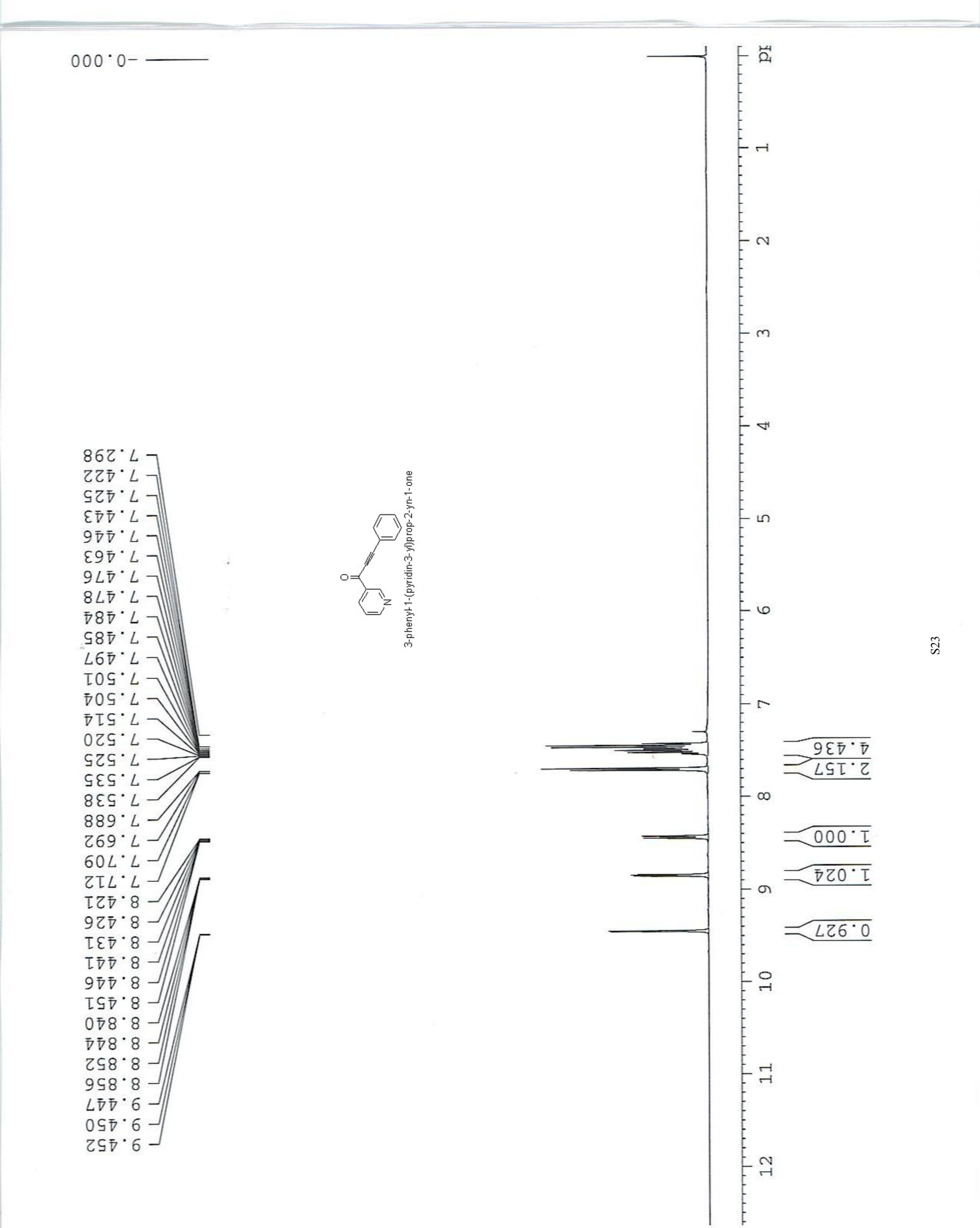
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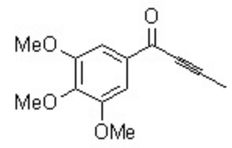
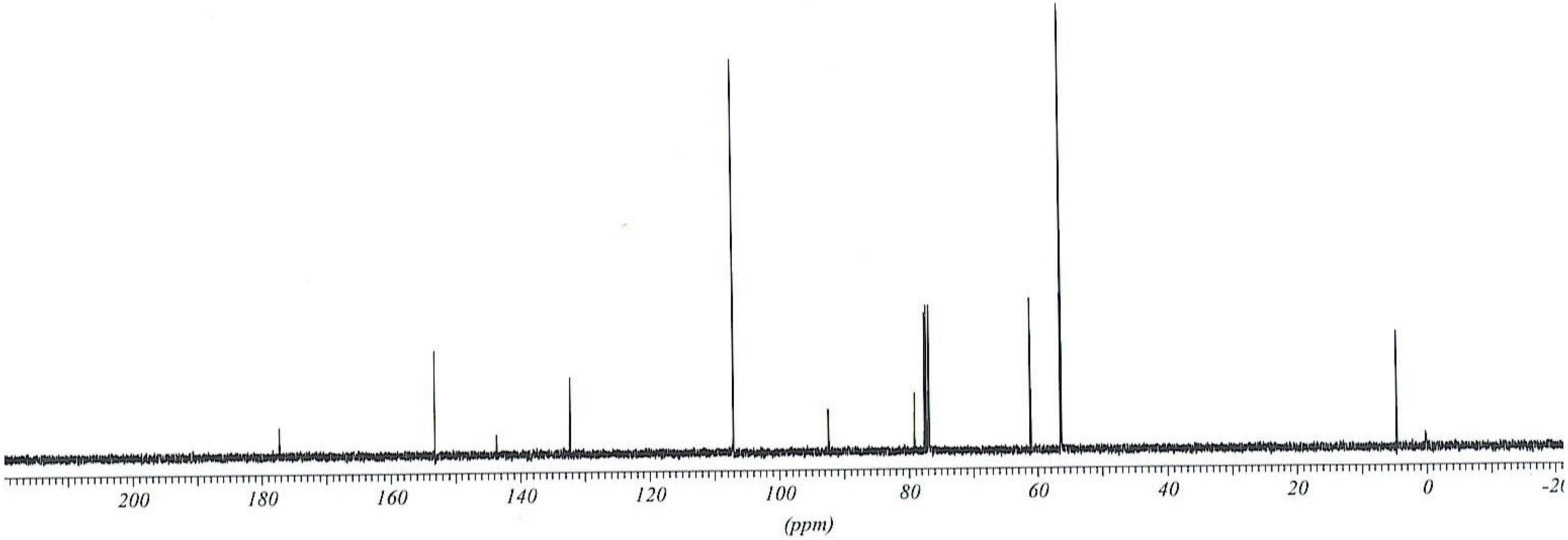


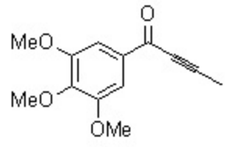
1-(3,4,5-trimethoxyphenyl)but-2-yn-1-one



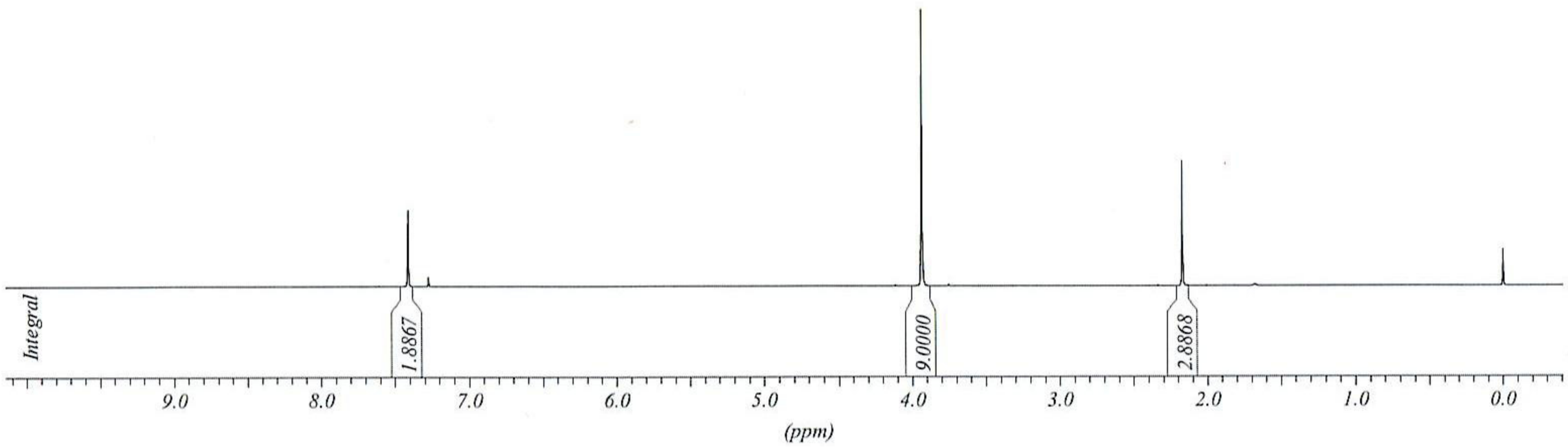
7.4111

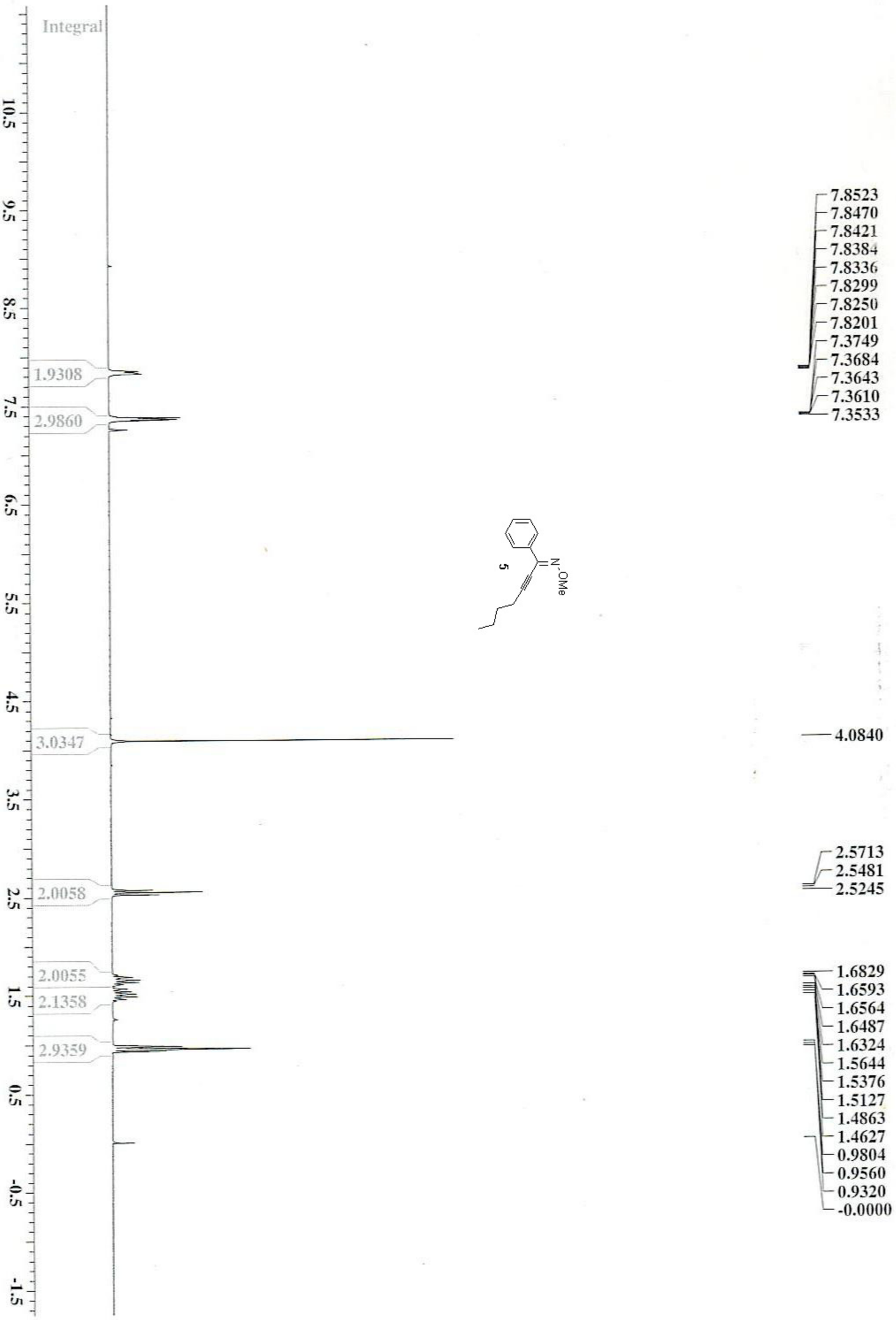
3.9365

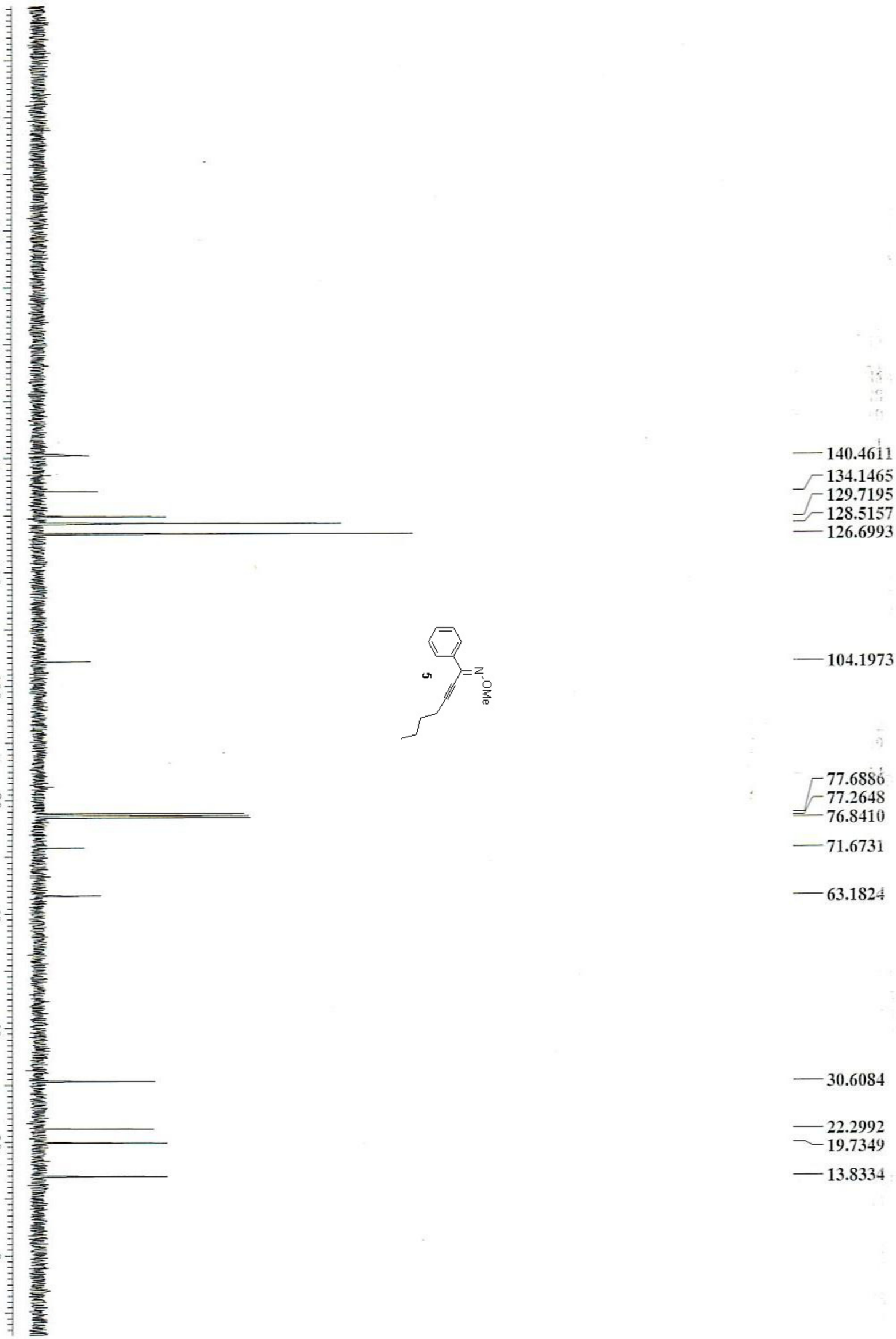
2.1711

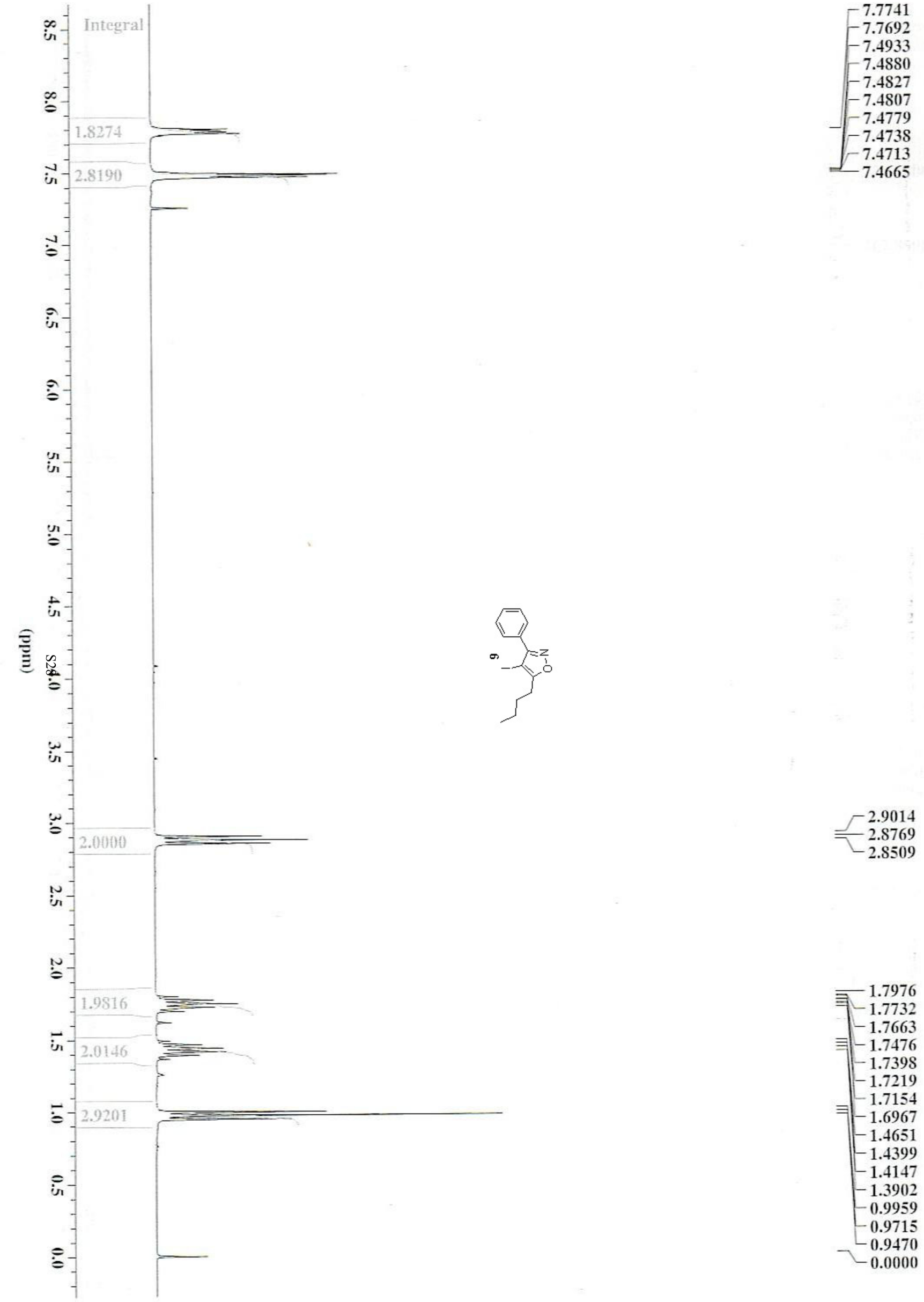


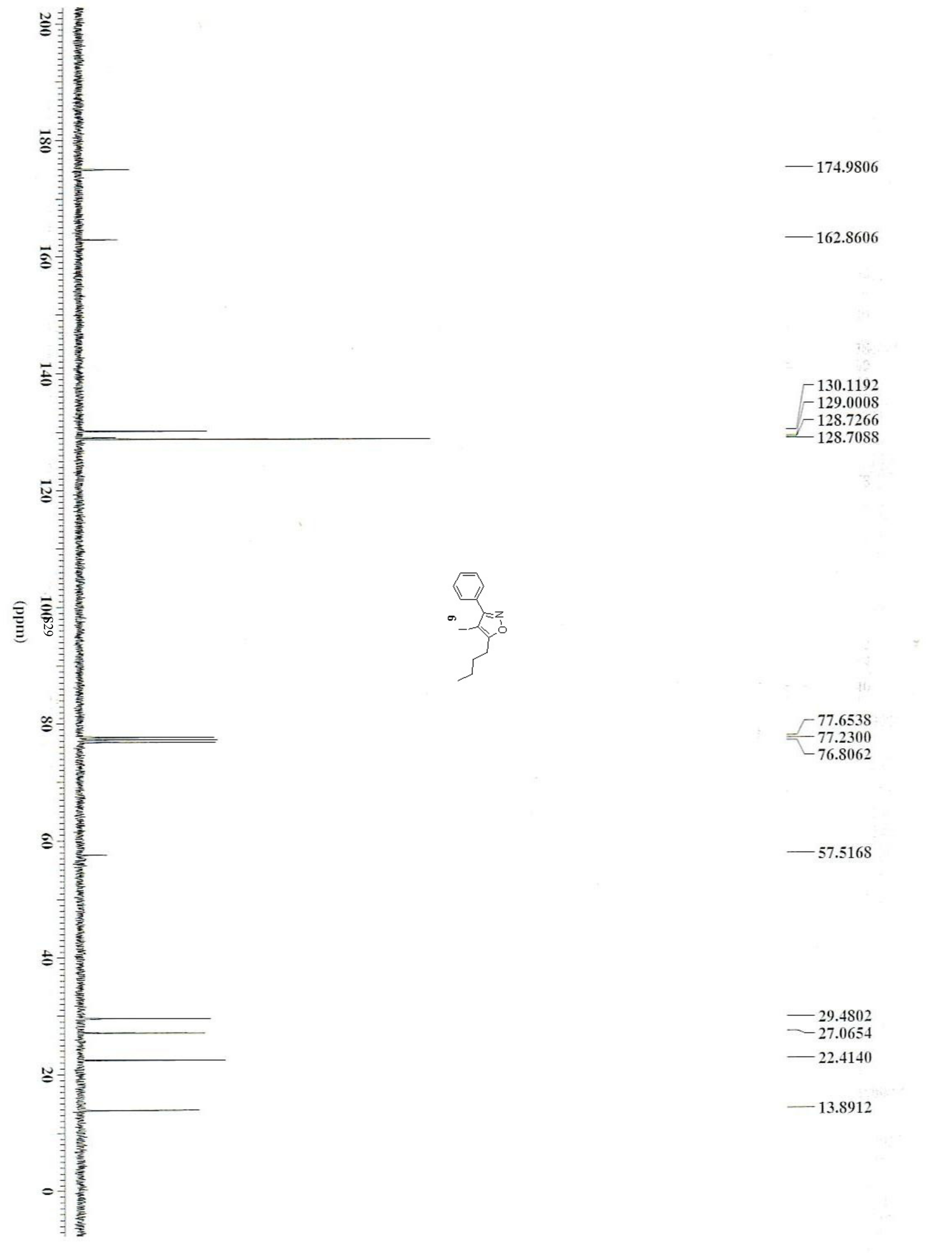
1-(3,4,5-trimethoxyphenyl)but-2-yn-1-one

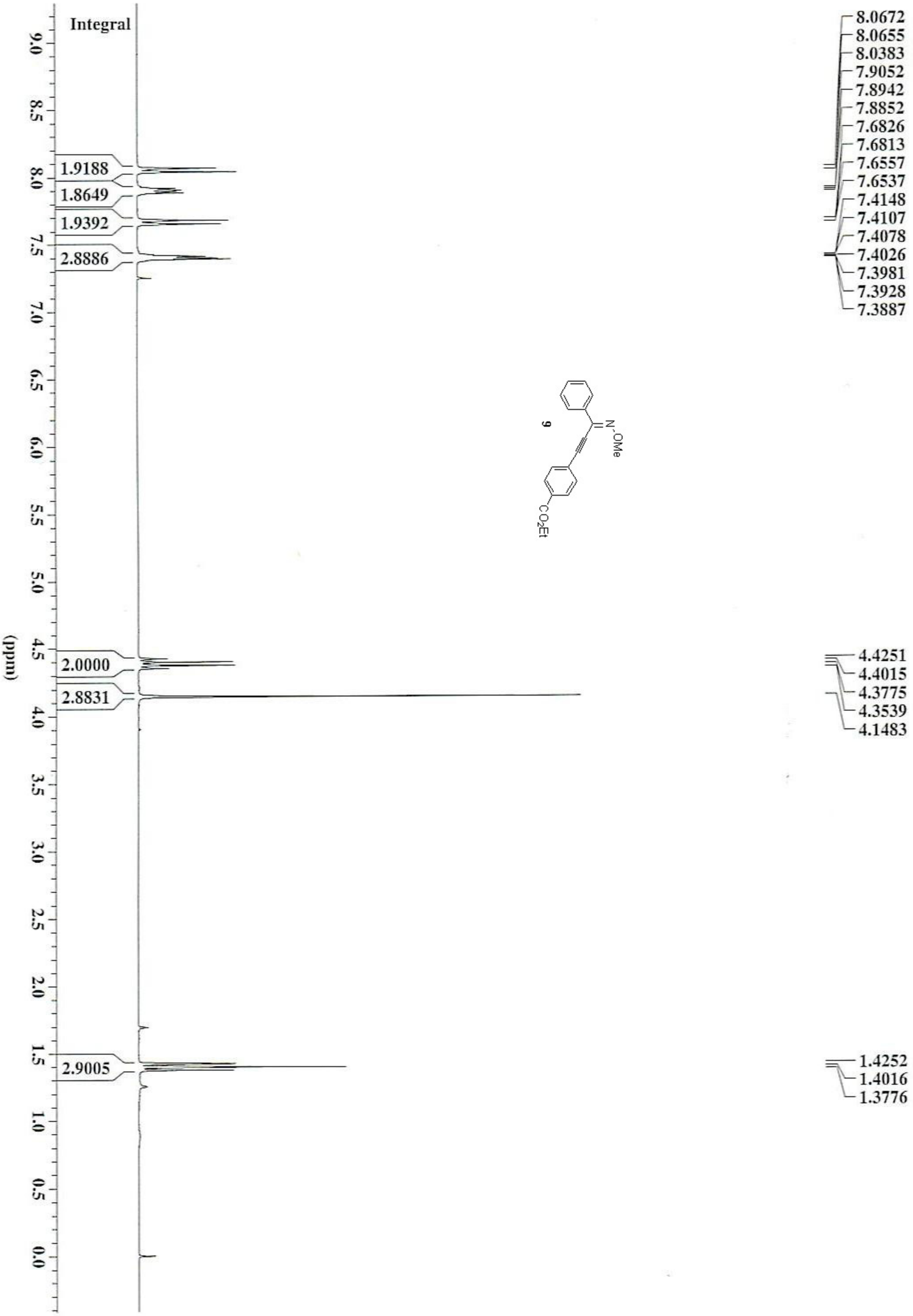


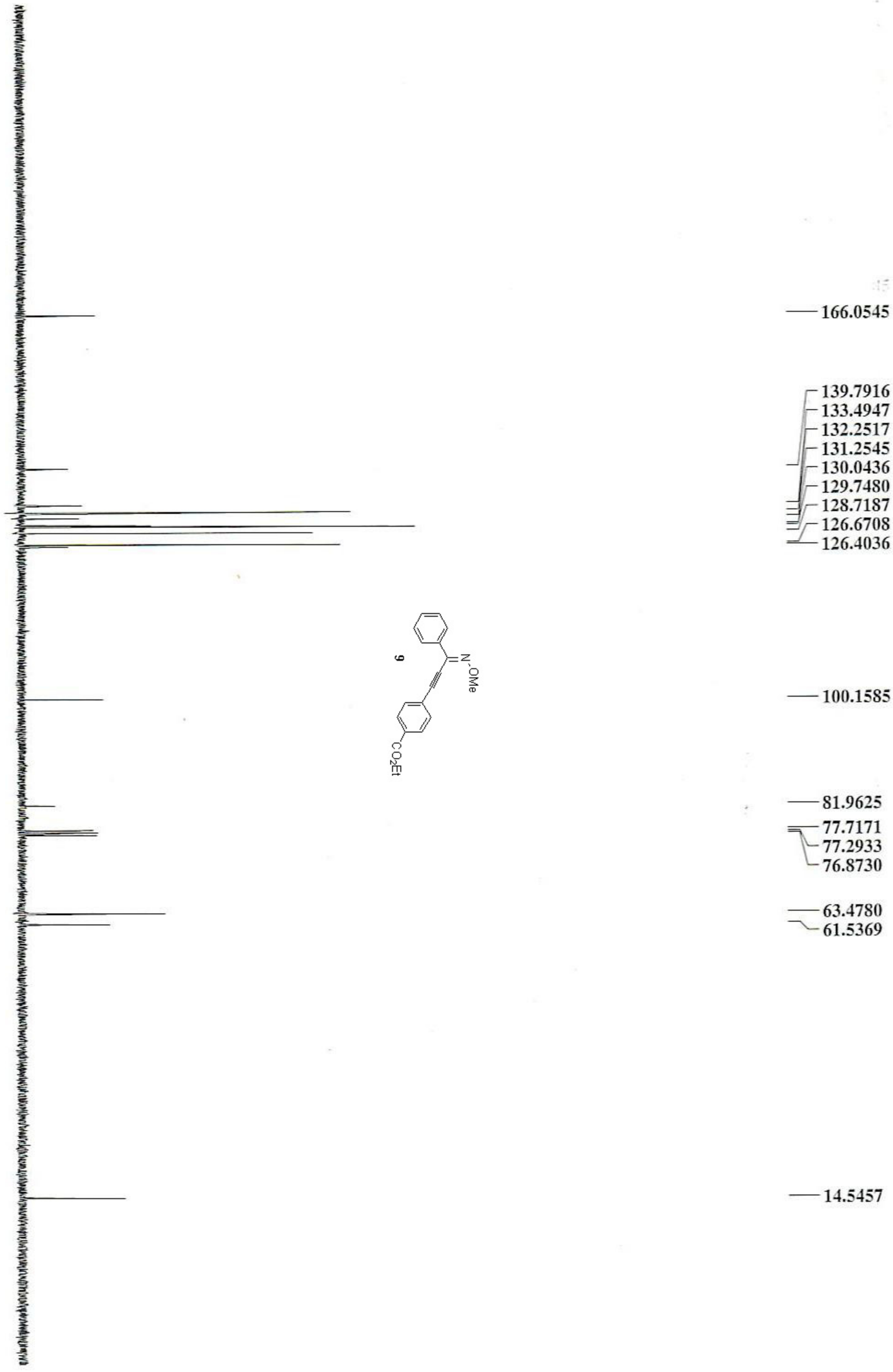

Integral
1.9308
2.9860
3.0347
2.0058
2.0055
2.1358
2.9359
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)
7.8523
7.8470
7.8421
7.8384
7.8336
7.8299
7.8250
7.8201
7.3749
7.3684
7.3643
7.3610
7.3533
4.0840
2.5713
2.5481
2.5245
1.6829
1.6593
1.6564
1.6487
1.6324
1.5644
1.5376
1.5127
1.4863
1.4627
0.9804
0.9560
0.9320
-0.0000
N-OMe
5

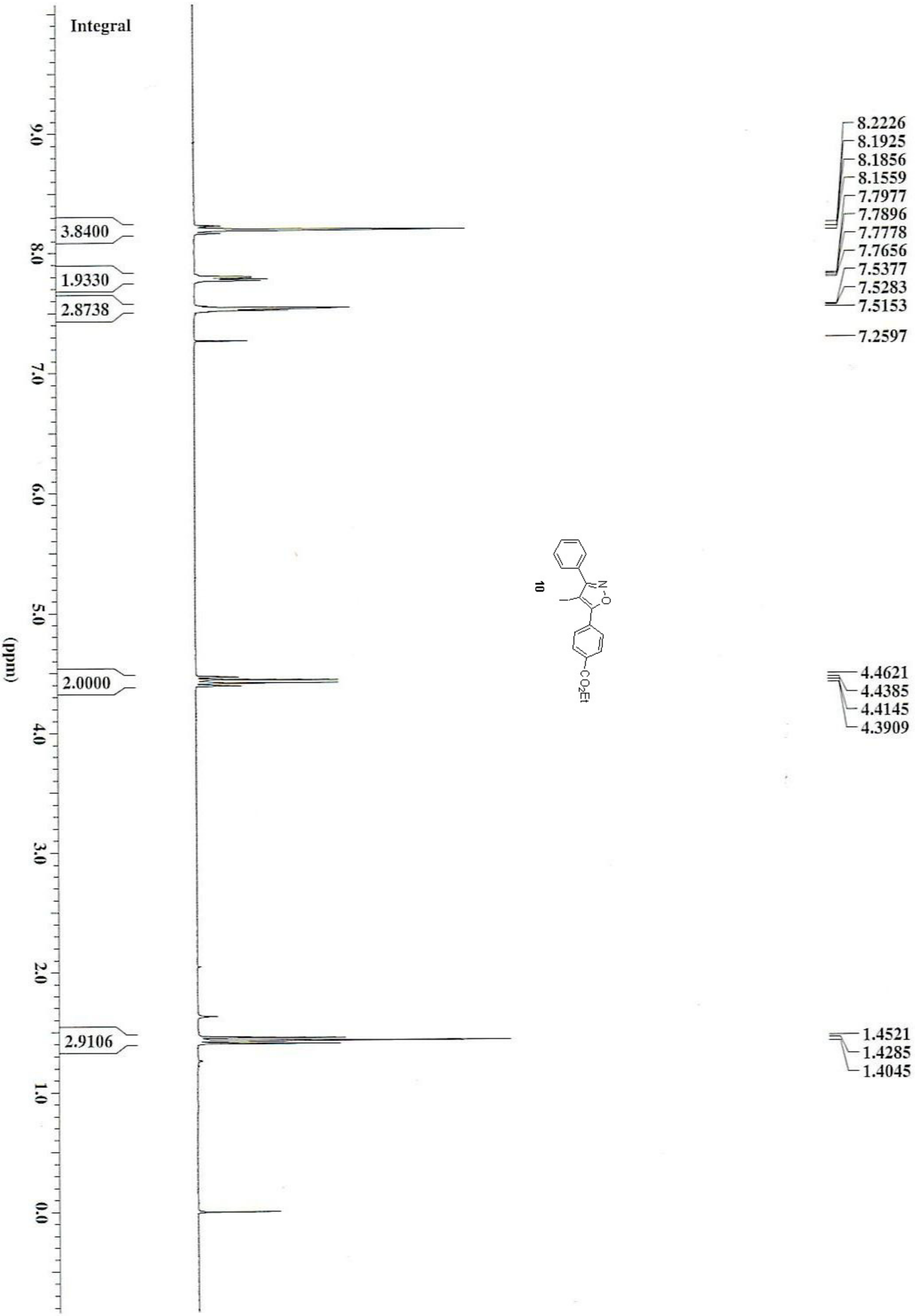

200
180
160
140
120
100
80
60
40
20
0
(ppm)
N
OMe
5
140.4611
134.1465
129.7195
128.5157
126.6993
104.1973
77.6886
77.2648
76.8410
71.6731
63.1824
30.6084
22.2992
19.7349
13.8334

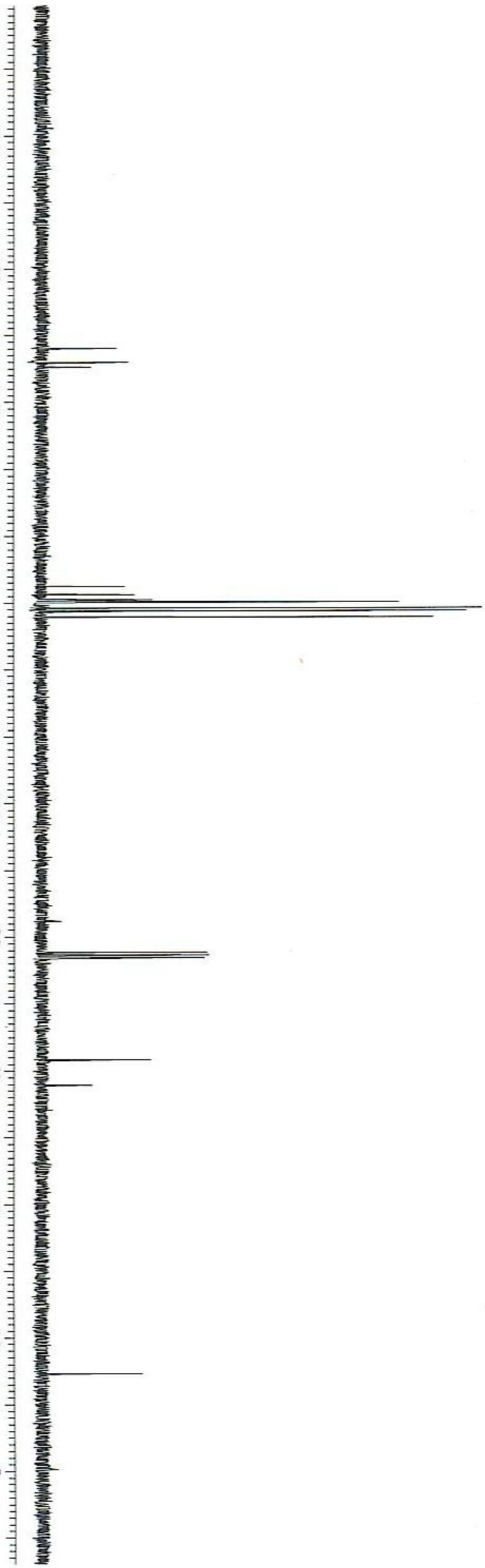

Integral
1.8274
2.8190
2.0000
1.9816
2.0146
2.9201
7.7741
7.7692
7.4933
7.4880
7.4827
7.4807
7.4779
7.4738
7.4713
7.4665
2.9014
2.8769
2.8509
1.7976
1.7732
1.7663
1.7476
1.7398
1.7219
1.7154
1.6967
1.4651
1.4399
1.4147
1.3902
0.9959
0.9715
0.9470
0.0000
N
O
9
6
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

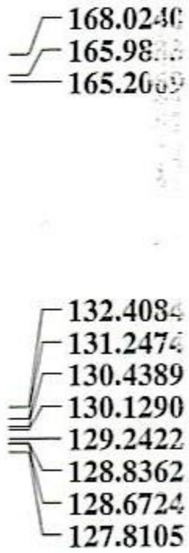

200
180
160
140
120
100
80
60
40
20
0
(ppm)
174.9806
162.8606
130.1192
129.0008
128.7266
128.7088
77.6538
77.2300
76.8062
57.5168
29.4802
27.0654
22.4140
13.8912
6
N
O

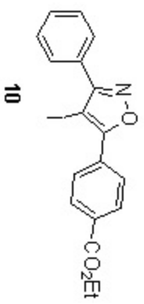

Integral
1.9188
1.8649
1.9392
2.8886
2.0000
2.8831
2.9005
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)
8.0672
8.0655
8.0383
7.9052
7.8942
7.8852
7.6826
7.6813
7.6557
7.6537
7.4148
7.4107
7.4078
7.4026
7.3981
7.3928
7.3887
9
N-OMe
CO2Et
4.4251
4.4015
4.3775
4.3539
4.1483
1.4252
1.4016
1.3776


200
180
160
140
120
100
80
60
40
20
0
(ppm)
N
OMe
9
CO2Et
166.0545
139.7916
133.4947
132.2517
131.2545
130.0436
129.7480
128.7187
126.6708
126.4036
100.1585
81.9625
77.7171
77.2933
76.8730
63.4780
61.5369
14.5457


Integral
3.8400
1.9330
2.8738
2.0000
2.9106
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
8.2226
8.1925
8.1856
8.1559
7.7977
7.7896
7.7778
7.7656
7.5377
7.5283
7.5153
7.2597
4.4621
4.4385
4.4145
4.3909
1.4521
1.4285
1.4045
10
N
O
CO2Et

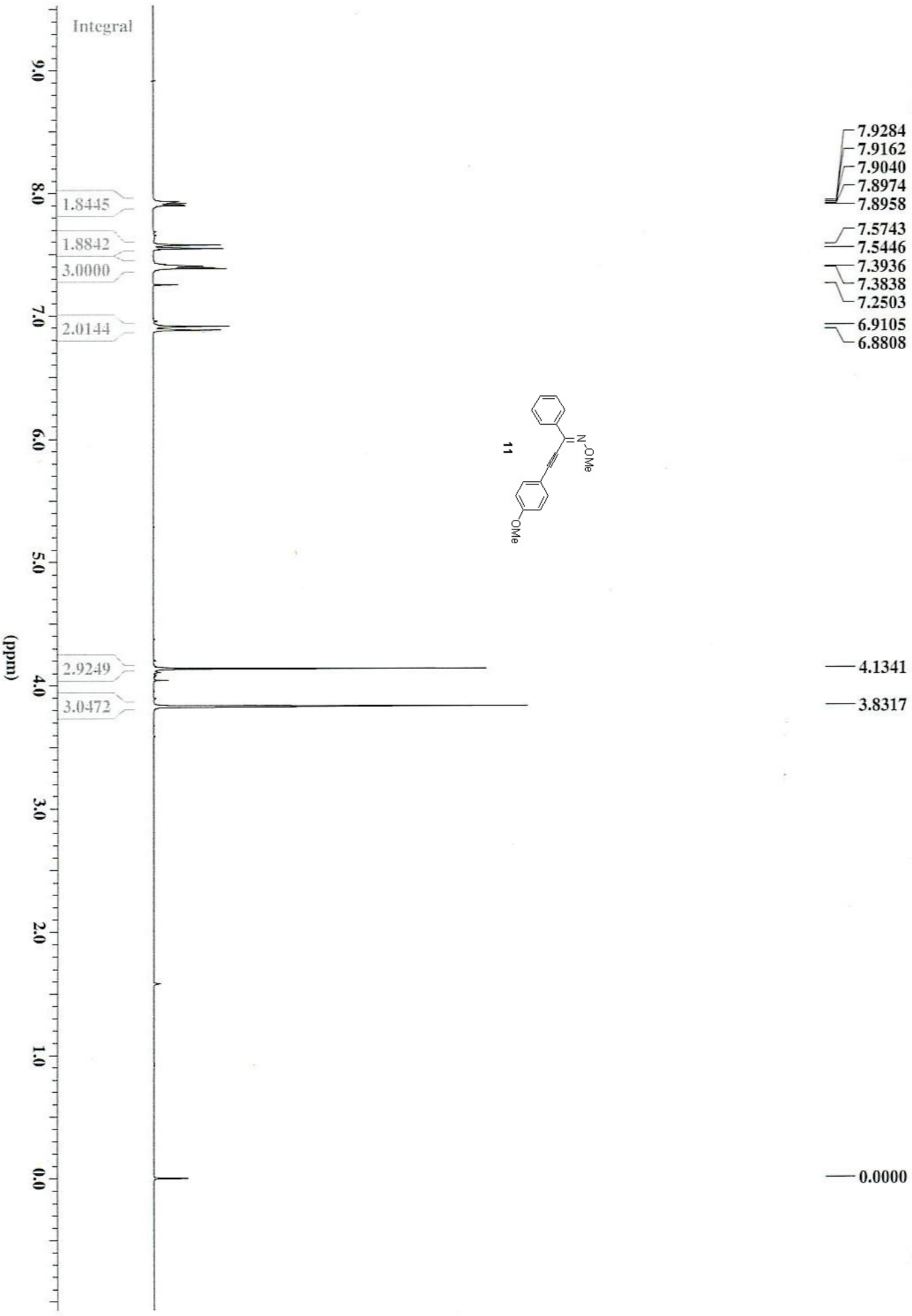

200
180
160
140
120
100
80
60
40
20
0
(ppm)

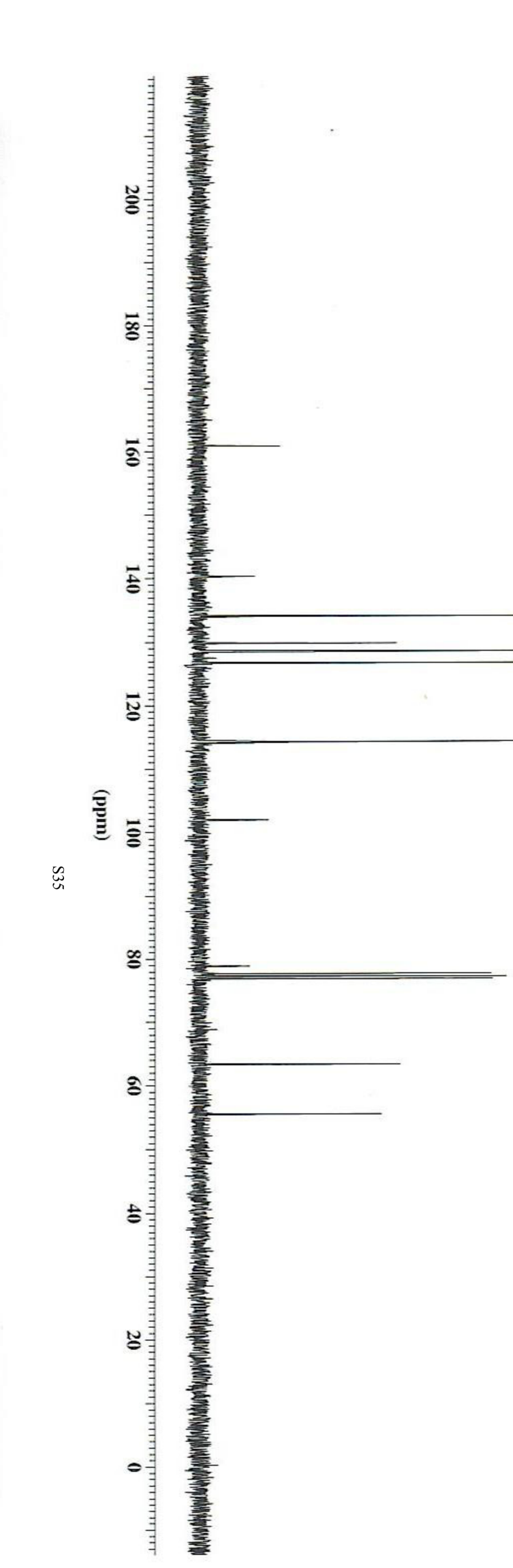

168.0240
165.9813
165.2069
132.4084
131.2474
130.4389
130.1290
129.2422
128.8362
128.6724
127.8105

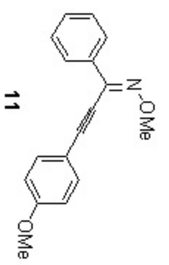

N
O
CO2Et

10


77.7029
77.2790
76.8552
61.6331
57.8151
14.5742


Integral
1.8445
1.8842
3.0000
2.0144
2.9249
3.0472
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
11
N
OMe
OMe
7.9284
7.9162
7.9040
7.8974
7.8958
7.5743
7.5446
7.3936
7.3838
7.2503
6.9105
6.8808
4.1341
3.8317
0.0000





11

160.8546

140.3614
134.0966
133.9791
129.8299
128.6189
126.7456

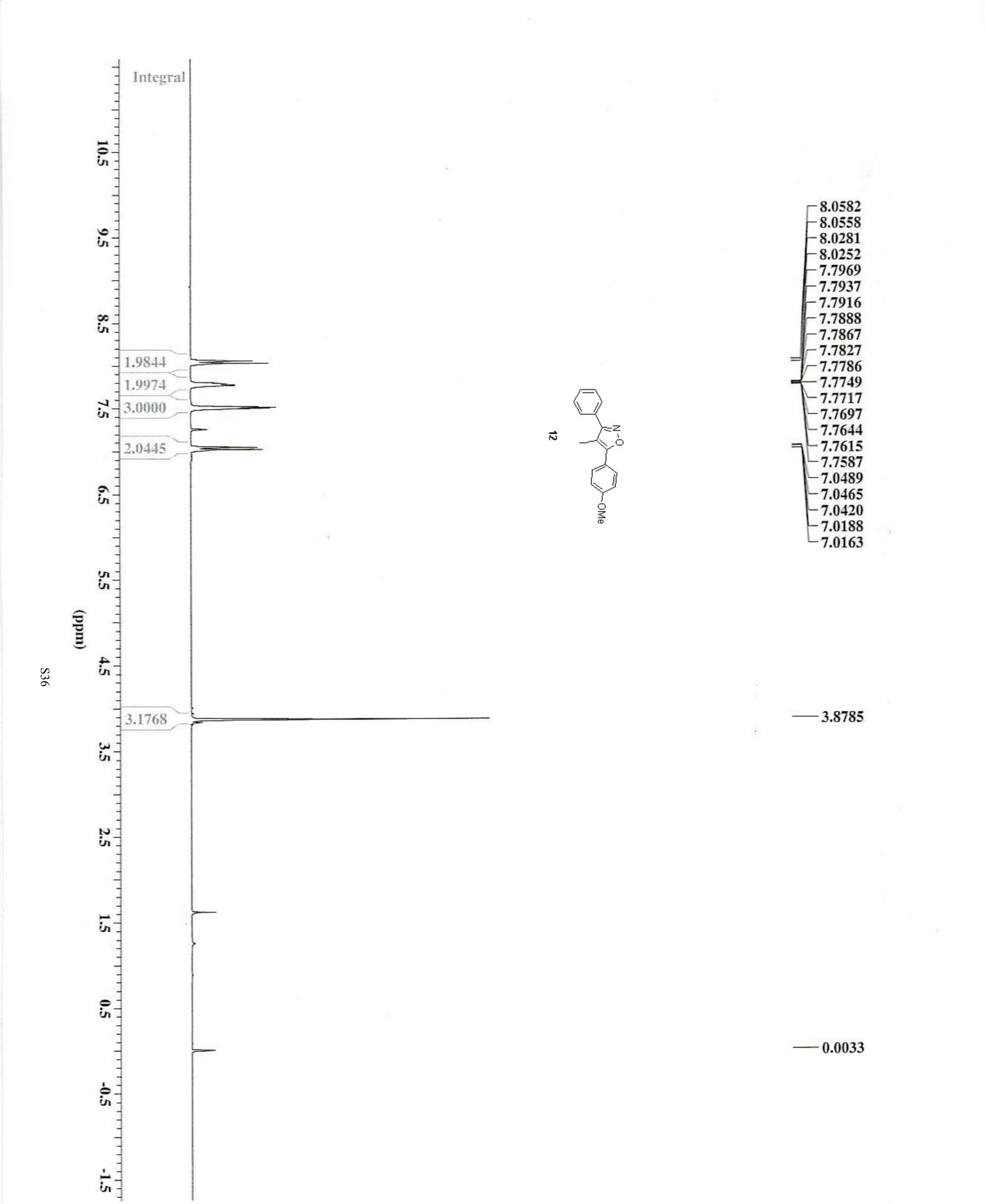
114.3406
113.9987

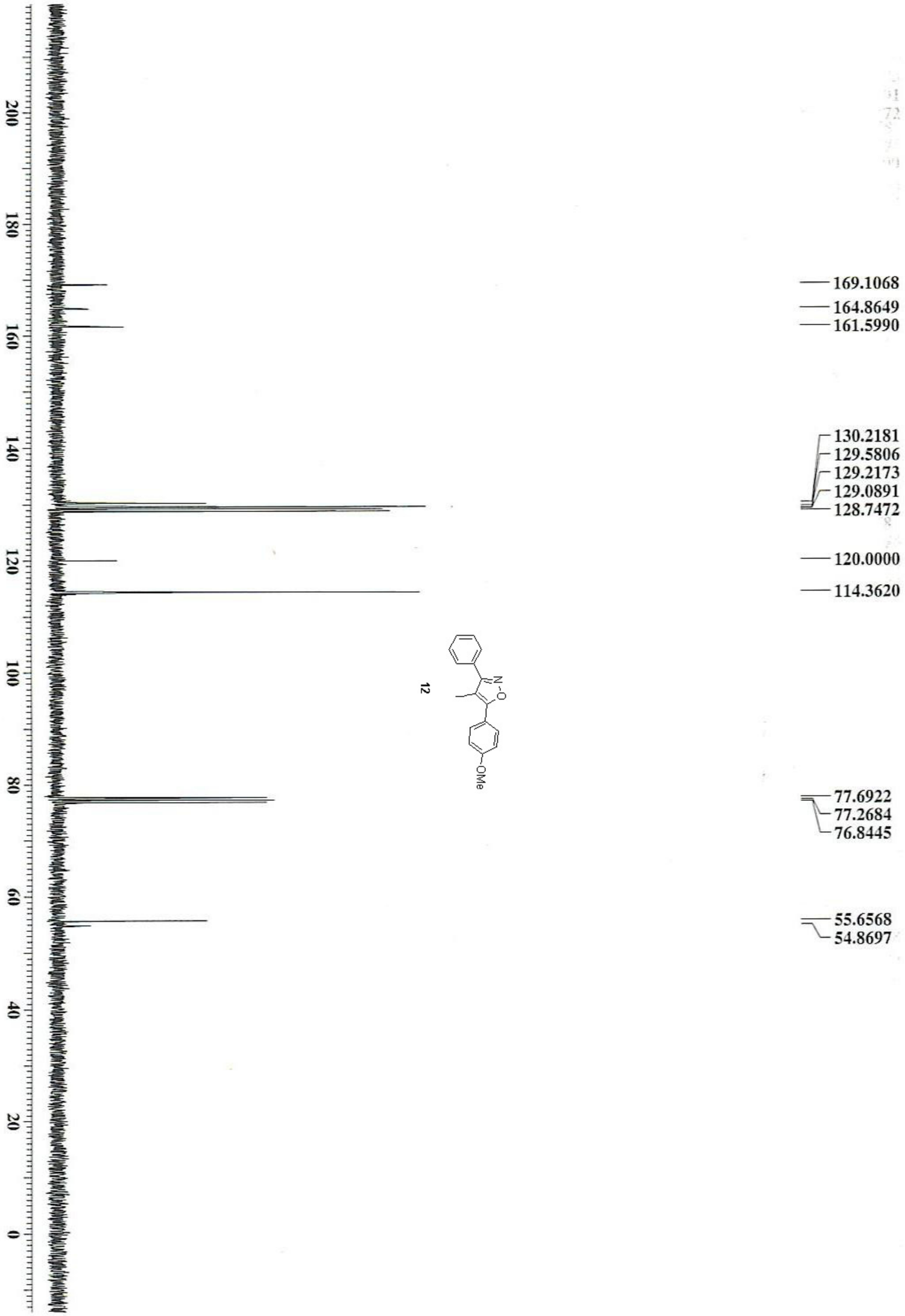
101.8823

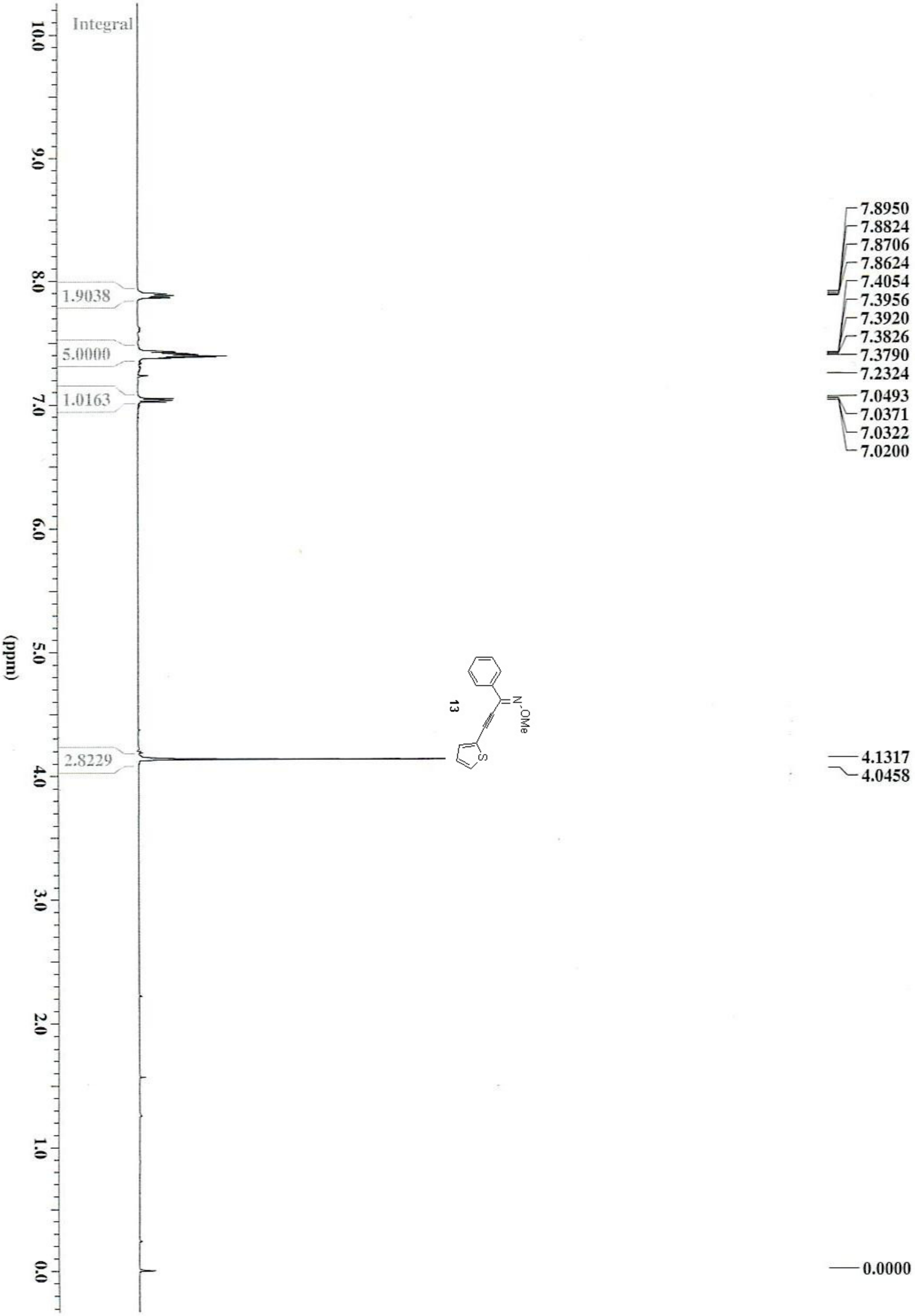
78.8354
77.6922
77.2684
76.8445

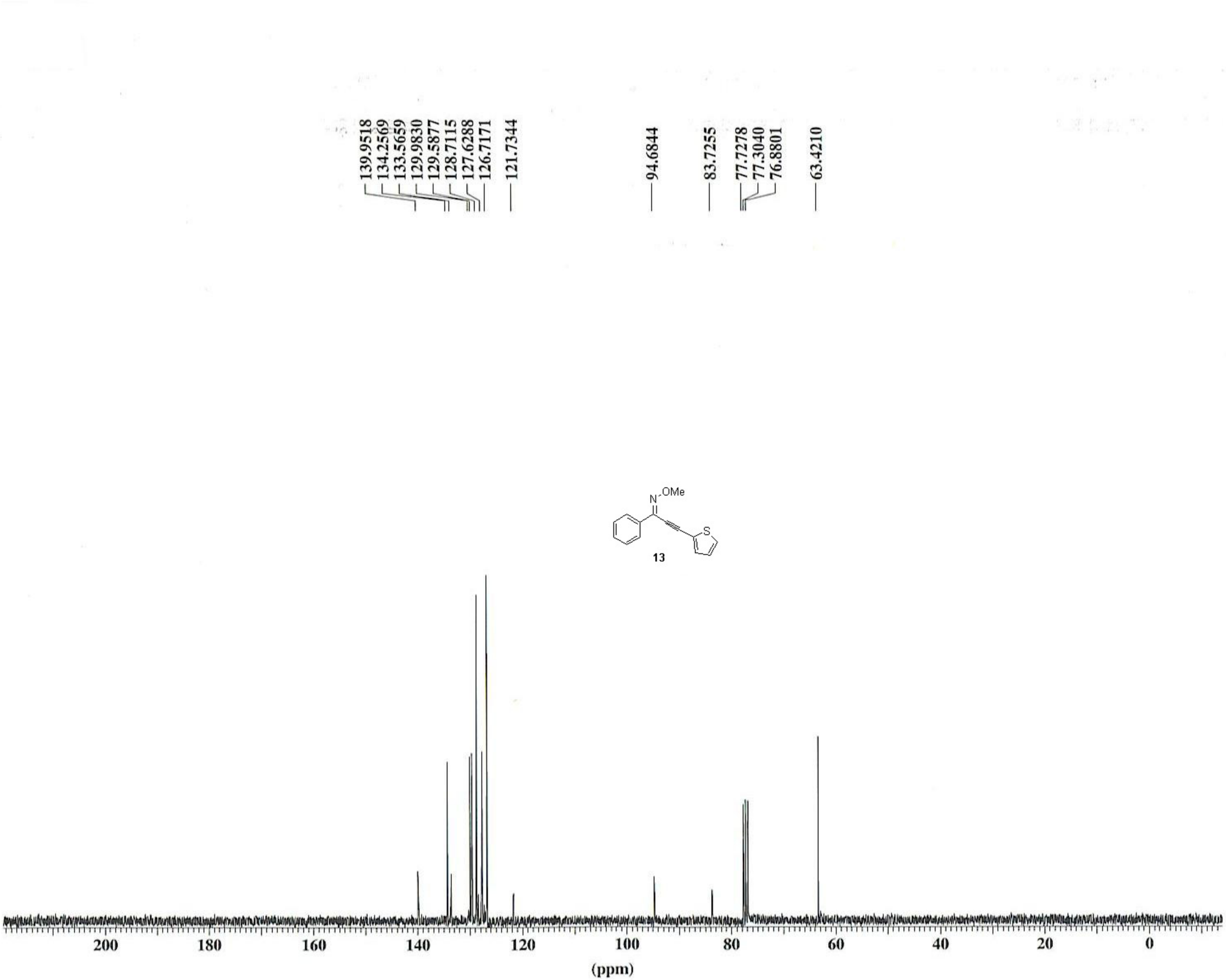
63.3106

55.5891


Integral
1.9844
1.9974
3.0000
2.0445
3.1768
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)
12
OMe
8.0582
8.0558
8.0281
8.0252
7.7969
7.7937
7.7916
7.7888
7.7867
7.7827
7.7786
7.7749
7.7717
7.7697
7.7644
7.7615
7.7587
7.0489
7.0465
7.0420
7.0188
7.0163
3.8785
0.0033


169.1068
164.8649
161.5990
130.2181
129.5806
129.2173
129.0891
128.7472
120.0000
114.3620
77.6922
77.2684
76.8445
55.6568
54.8697
12
OMe
200
180
160
140
120
100
80
60
40
20
0
(ppm)

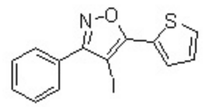

Integral
1.9038
5.0000
1.0163
2.8229
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
7.8950
7.8824
7.8706
7.8624
7.4054
7.3956
7.3920
7.3826
7.3790
7.2324
7.0493
7.0371
7.0322
7.0200
4.1317
4.0458
0.0000
13
N
OMe
S


139.9518
134.2569
133.5659
129.9830
129.5877
128.7115
127.6288
126.7171
121.7344
94.6844
83.7255
77.7278
77.3040
76.8801
63.4210
N
OMe
S
13
200
180
160
140
120
100
80
60
40
20
0
(ppm)

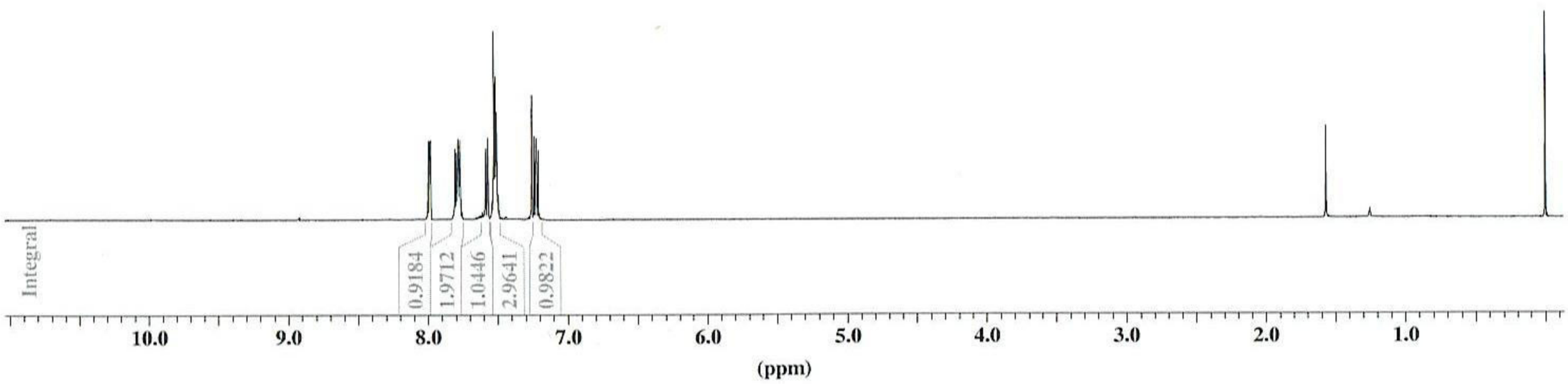
jw-106-H1

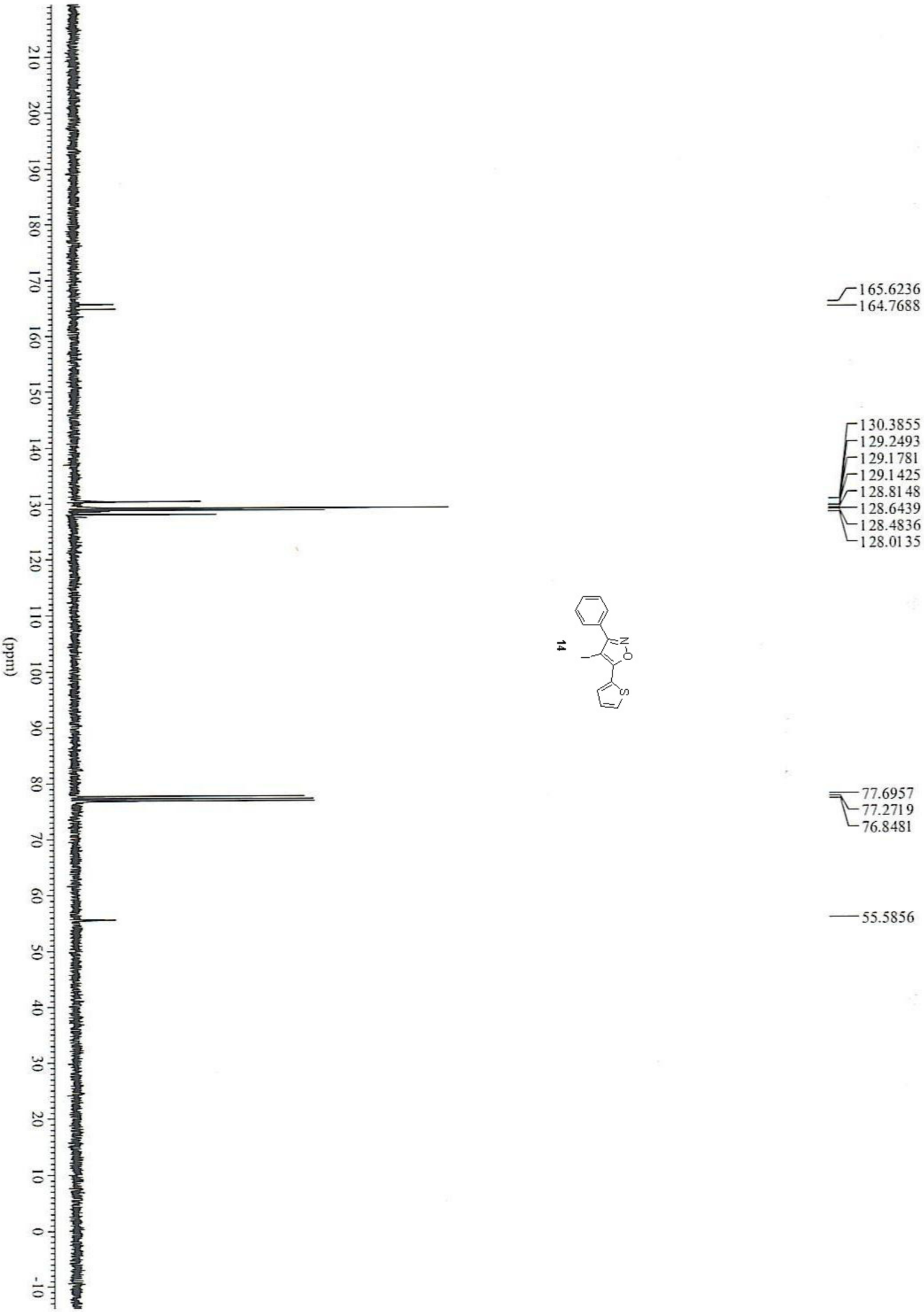
7.9984
7.9943
7.9858
7.9817
7.8034
7.7949
7.7831
7.7709
7.5702
7.5267
7.5169
7.5043
7.2565
7.2369
7.2243

-0.0000



14





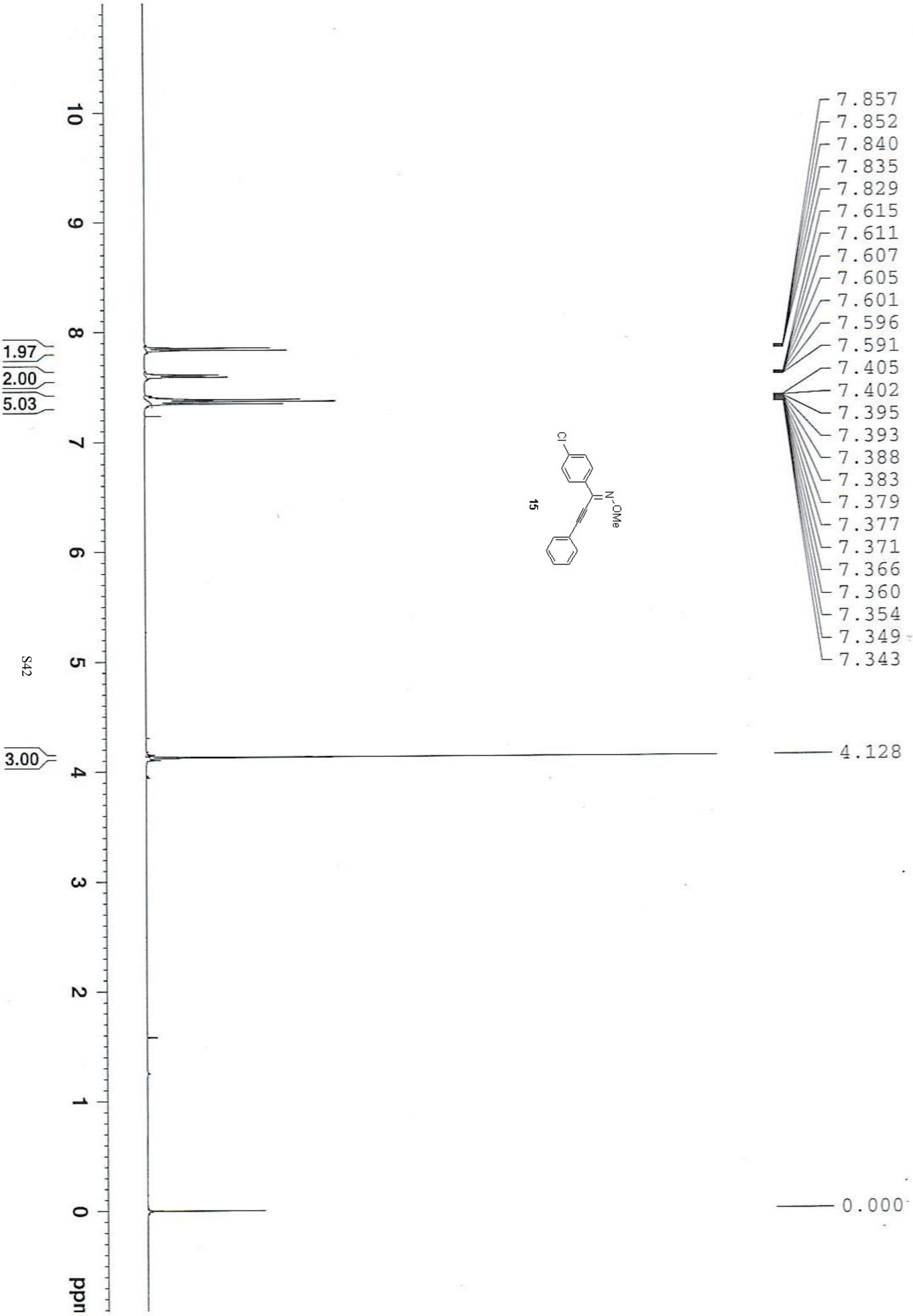
14

165.6236
164.7688

130.3855
129.2493
129.1781
129.1425
128.8148
128.6439
128.4836
128.0135

77.6957
77.2719
76.8481

55.5856


7.857
7.852
7.840
7.835
7.829
7.615
7.611
7.607
7.605
7.601
7.596
7.591
7.405
7.402
7.395
7.393
7.388
7.383
7.379
7.377
7.371
7.366
7.360
7.354
7.349
7.343
4.128
0.000
1.97
2.00
5.03
3.00
10
9
8
7
6
5
4
3
2
1
0
ppm
Cl
N
OMe

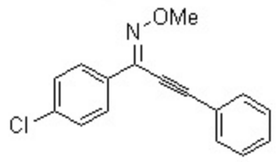
15

139.009
135.793
132.320
132.222
129.850
128.794
128.652
127.880
121.698

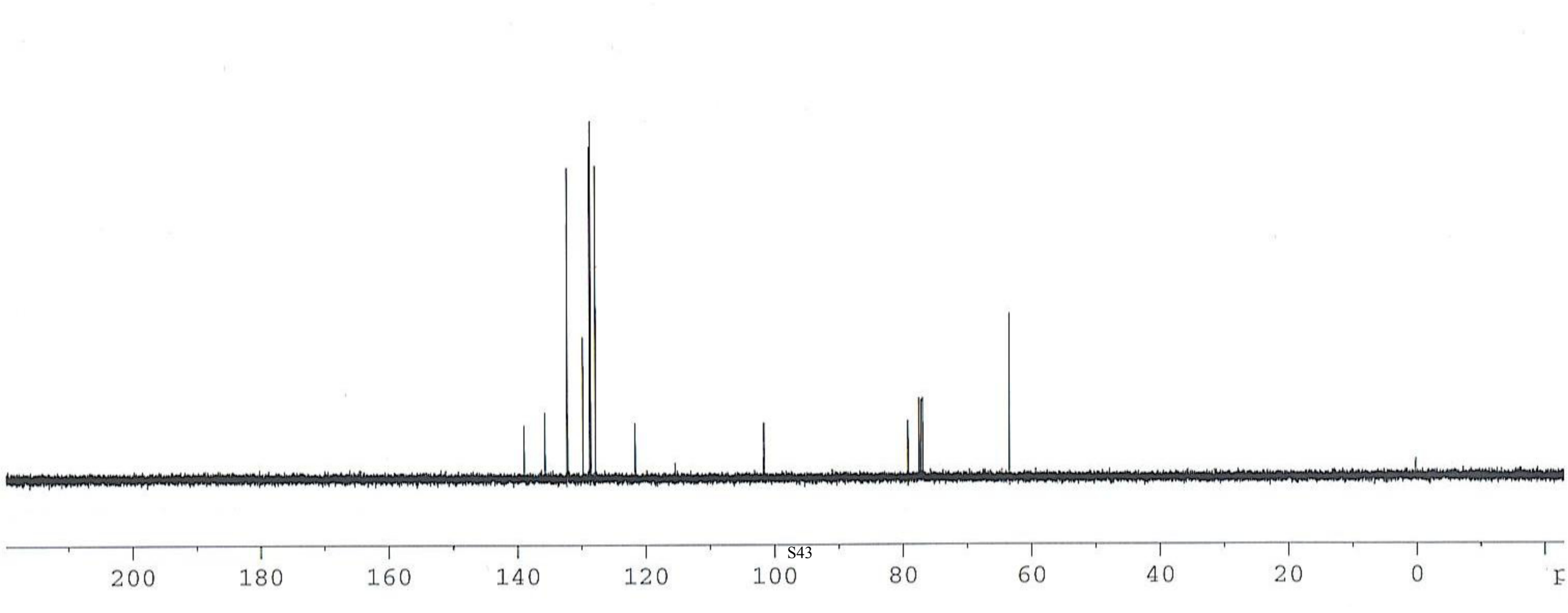
101.691

79.199
77.545
77.228
76.911

63.437

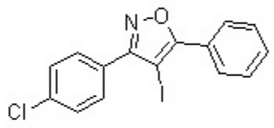


15

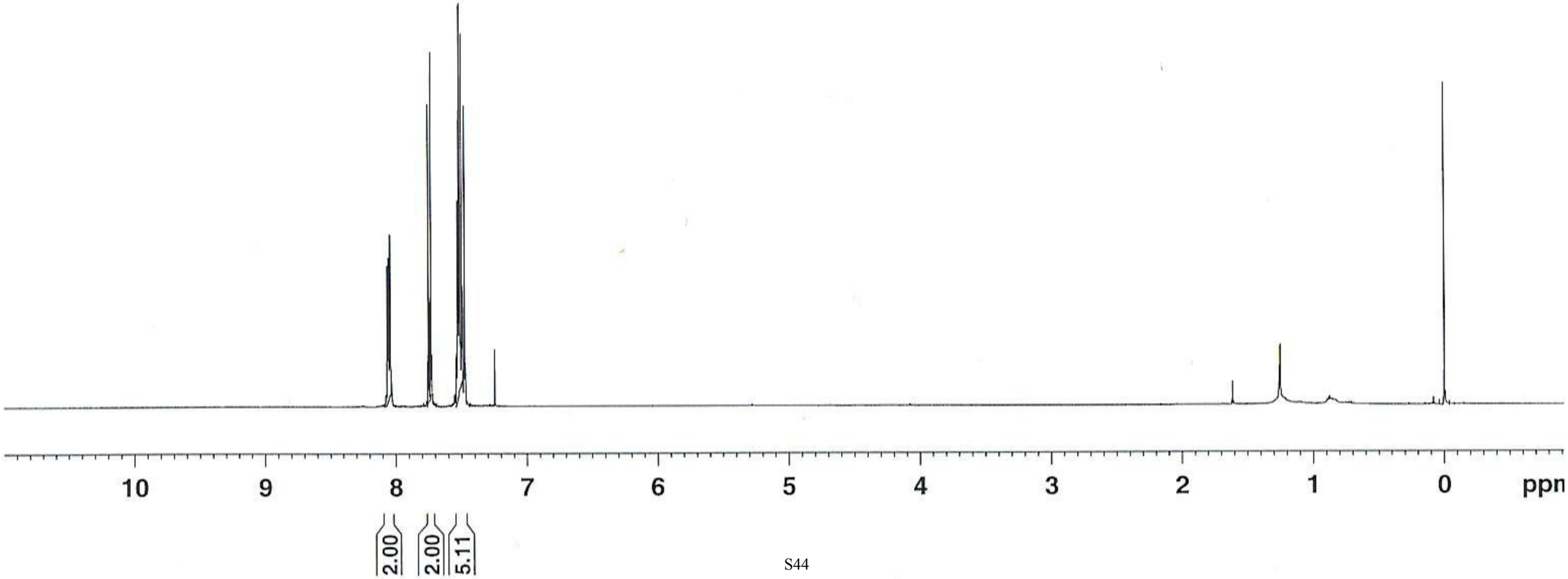


8.066
8.064
8.061
8.057
8.055
8.048
8.042
7.754
7.748
7.737
7.732
7.530
7.527
7.525
7.519
7.513
7.499
7.494
7.482
7.477

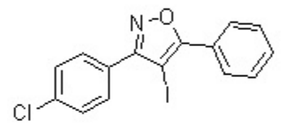
0.000



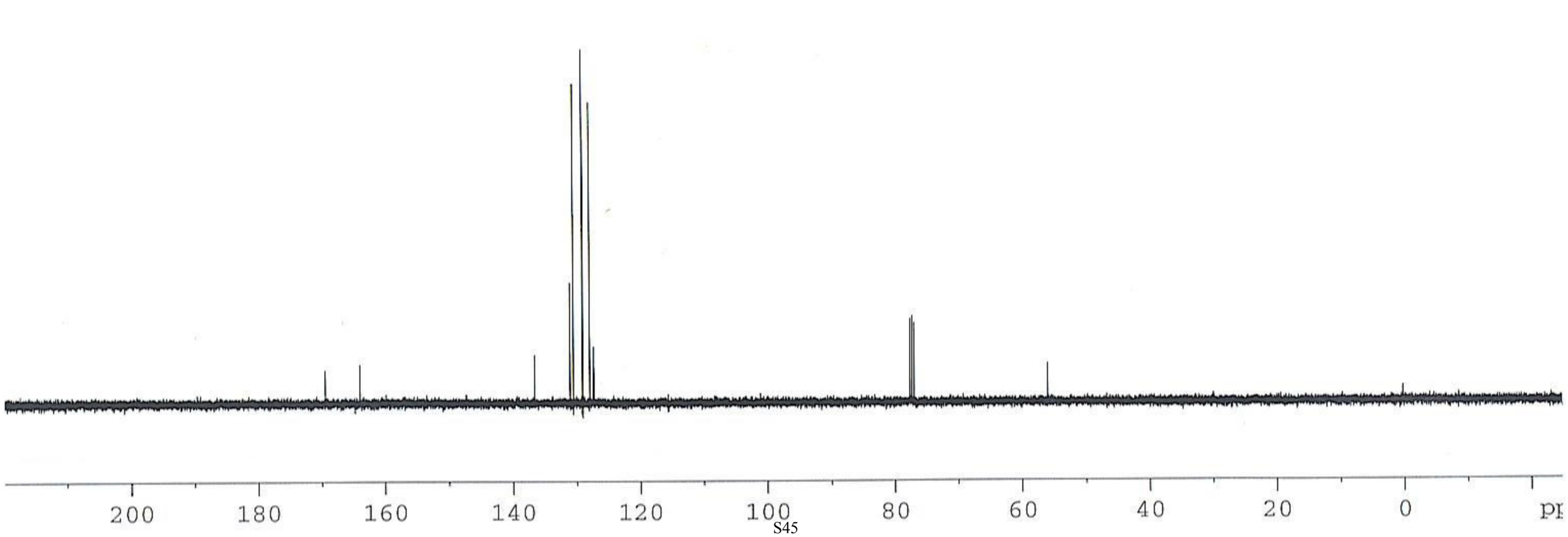
16

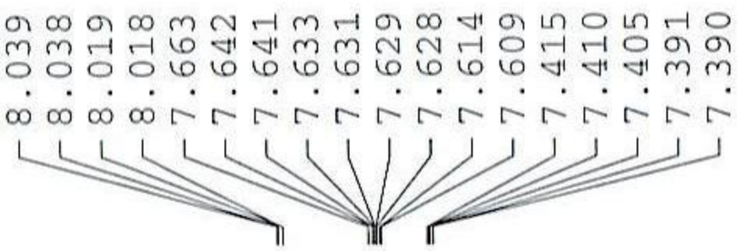


163.990
136.589
131.085
130.547
129.137
129.029
128.003
127.410
127.309
77.626
77.308
76.991
56.016

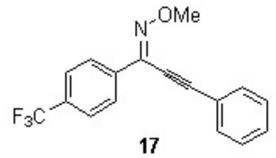


16

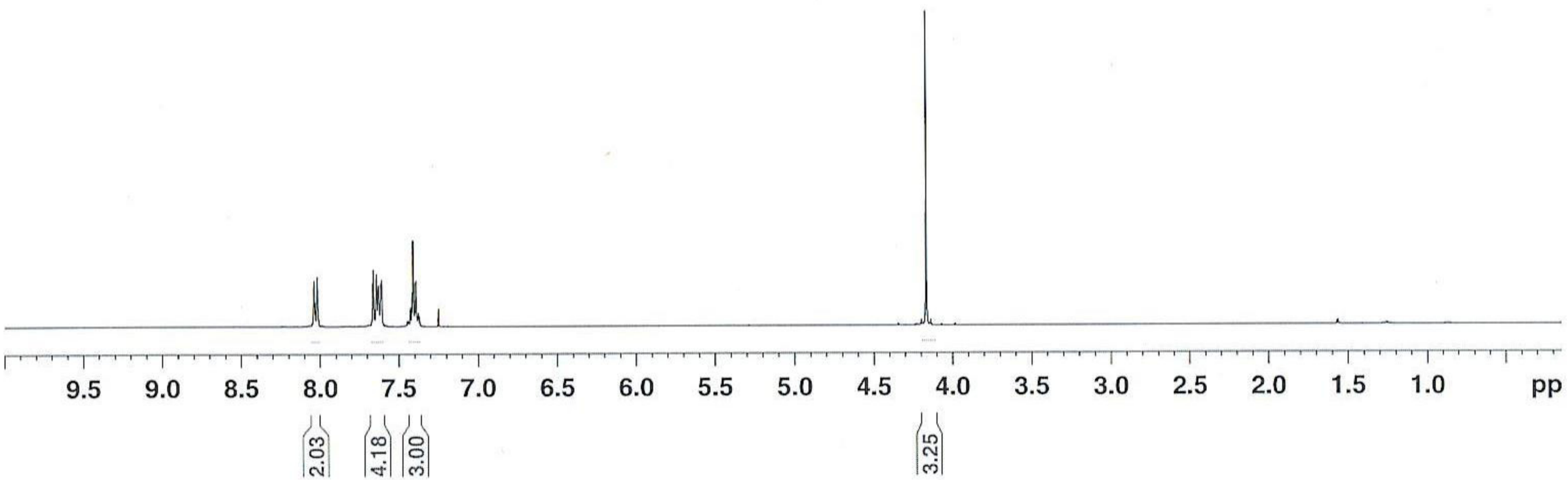



8.039
8.038
8.019
8.018
7.663
7.642
7.641
7.633
7.631
7.629
7.628
7.614
7.609
7.415
7.410
7.405
7.391
7.390

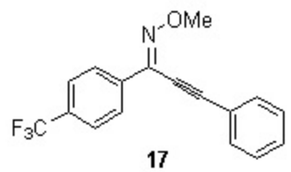

4.167


N
OMe
F3C

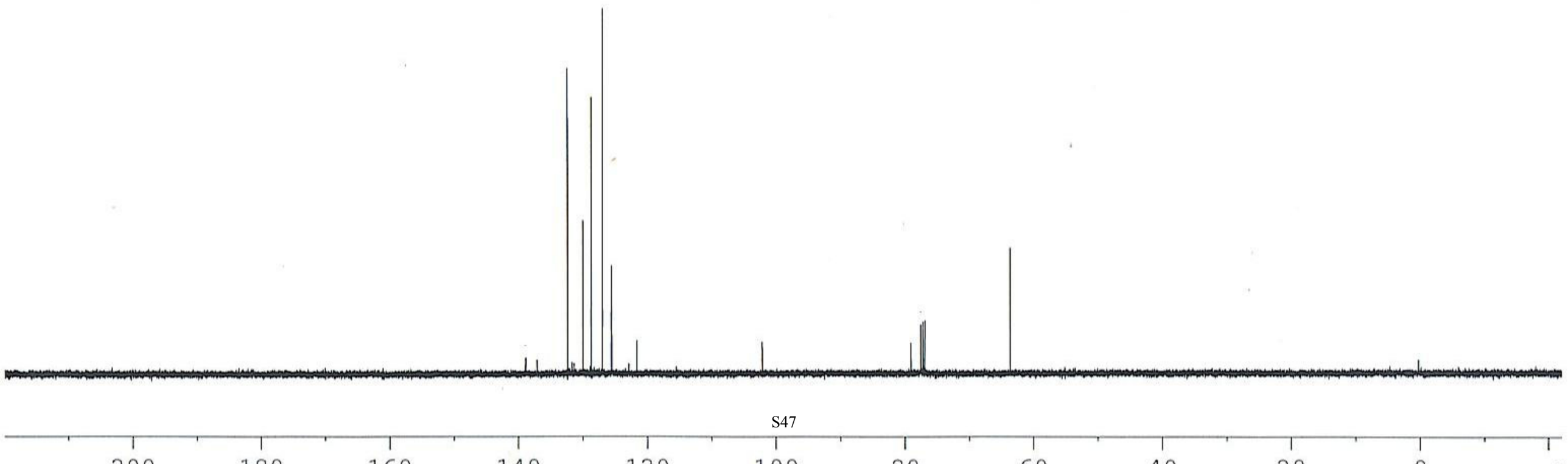
17

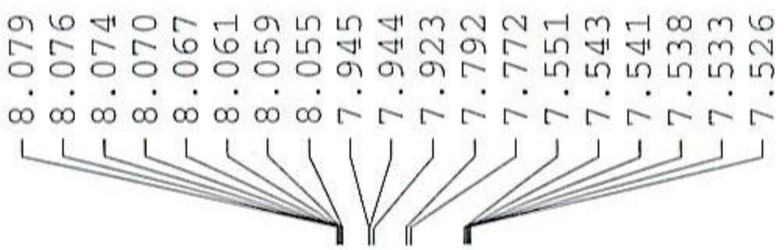

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
pp
2.03
4.18
3.00
3.25

138.915
137.151
132.427
132.419
132.409
132.398
132.390
130.033
128.768
128.758
128.750
126.990
126.963
126.953
126.945
125.649
125.611
125.573
125.535
121.649
102.159
79.095
77.587
77.270
76.951
63.686



17

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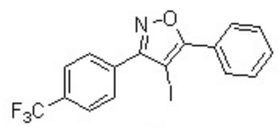
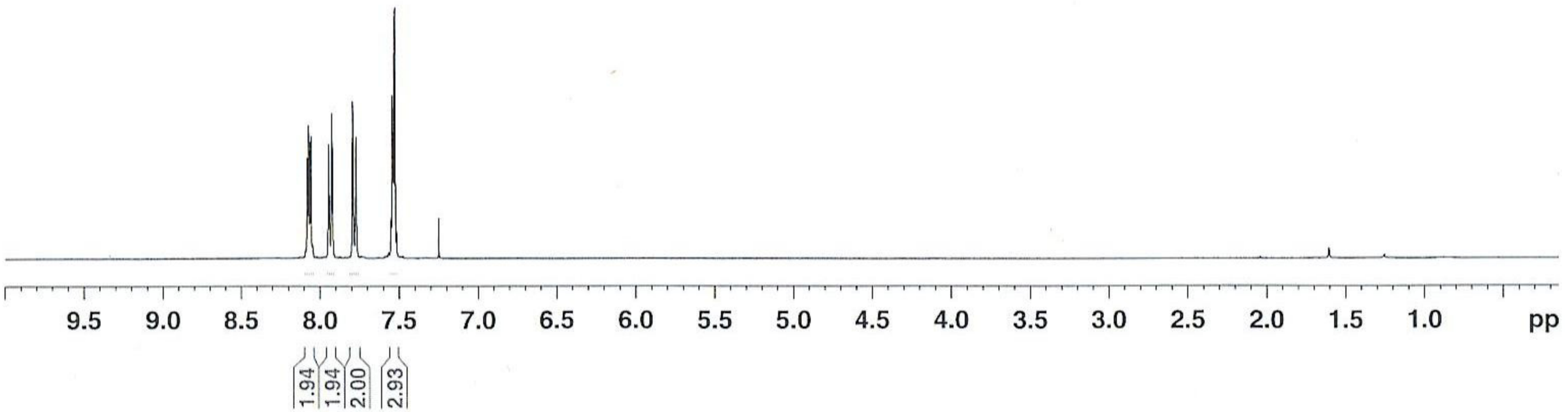
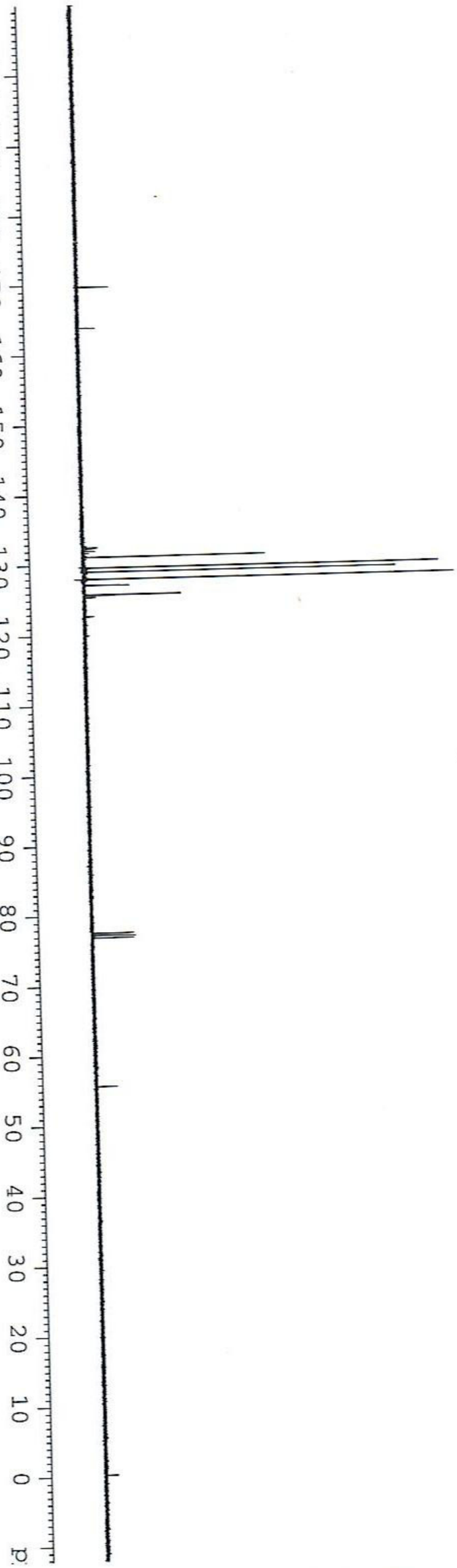
8.076
8.074
8.070
8.067
8.061
8.059
8.055
7.945
7.944
7.923
7.792
7.772
7.551
7.543
7.541
7.538
7.533
7.526

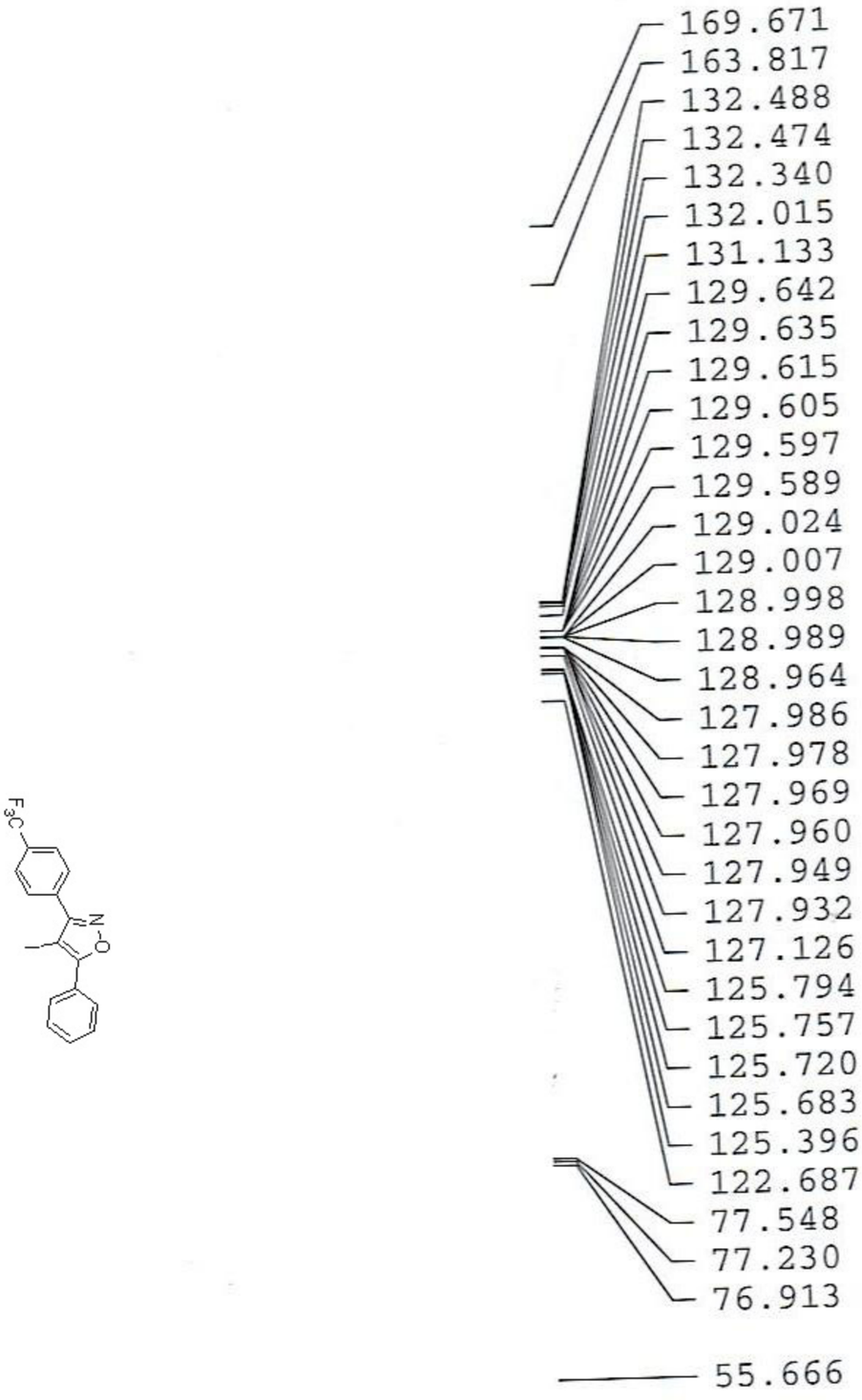

N
O
F3C
I

18


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
pp
1.94
1.94
2.00
2.93


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
p.

18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163.817
132.488
132.474
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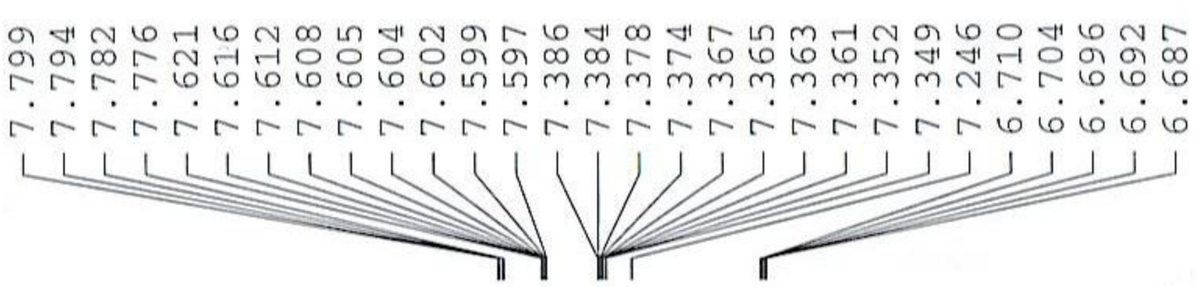
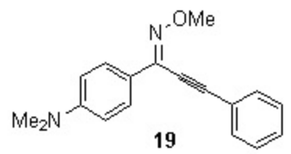
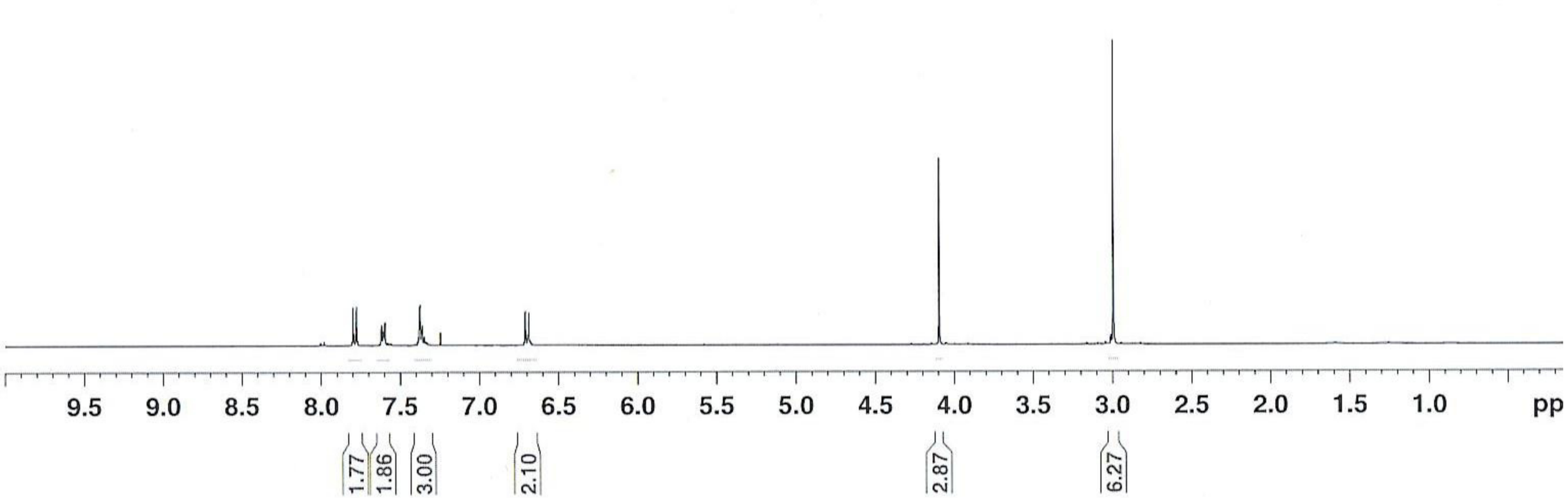
132.015
131.133
129.642
129.635
129.615
129.605
129.597
129.589
129.024
129.007
128.998
128.989
128.964
127.986
127.978
127.969
127.960
127.949
127.932
127.126
125.794
125.757
125.720
125.683
125.396
122.687
77.548
77.230
76.913
55.666



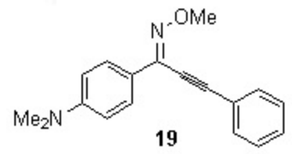
Current Data Paramete
NAME jw-276.f
EXPNO
PROCNO



19



151.614
140.324
132.367
129.531
128.617
127.825
122.308
111.909
100.484
80.158
77.613
77.295
76.978
63.033
40.553



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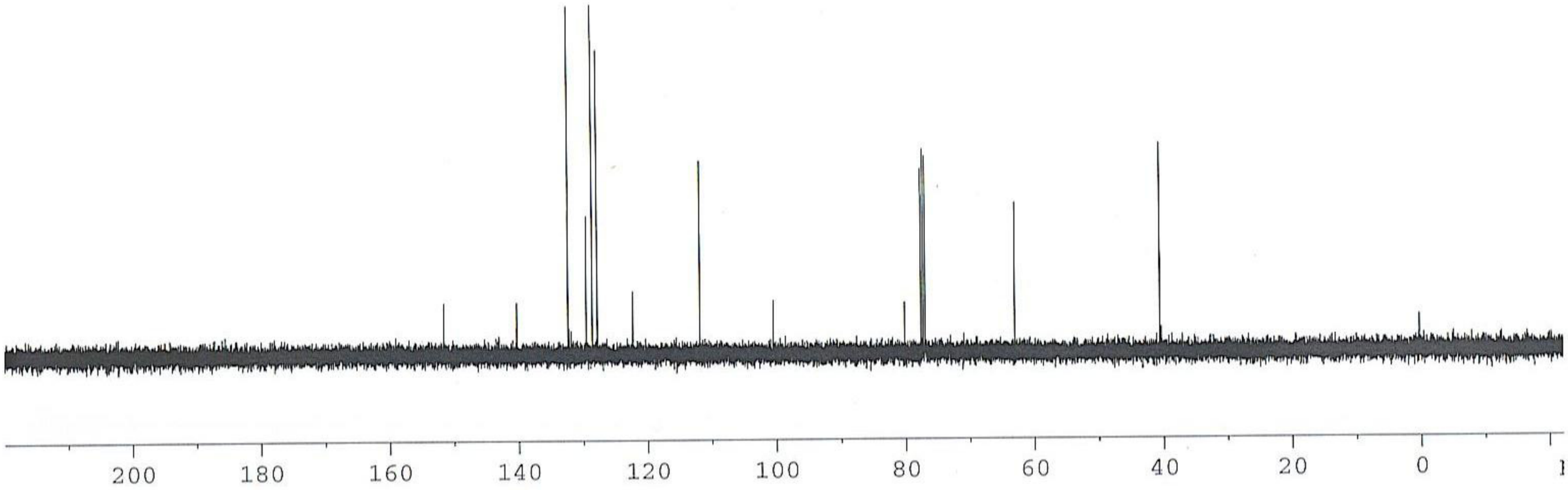
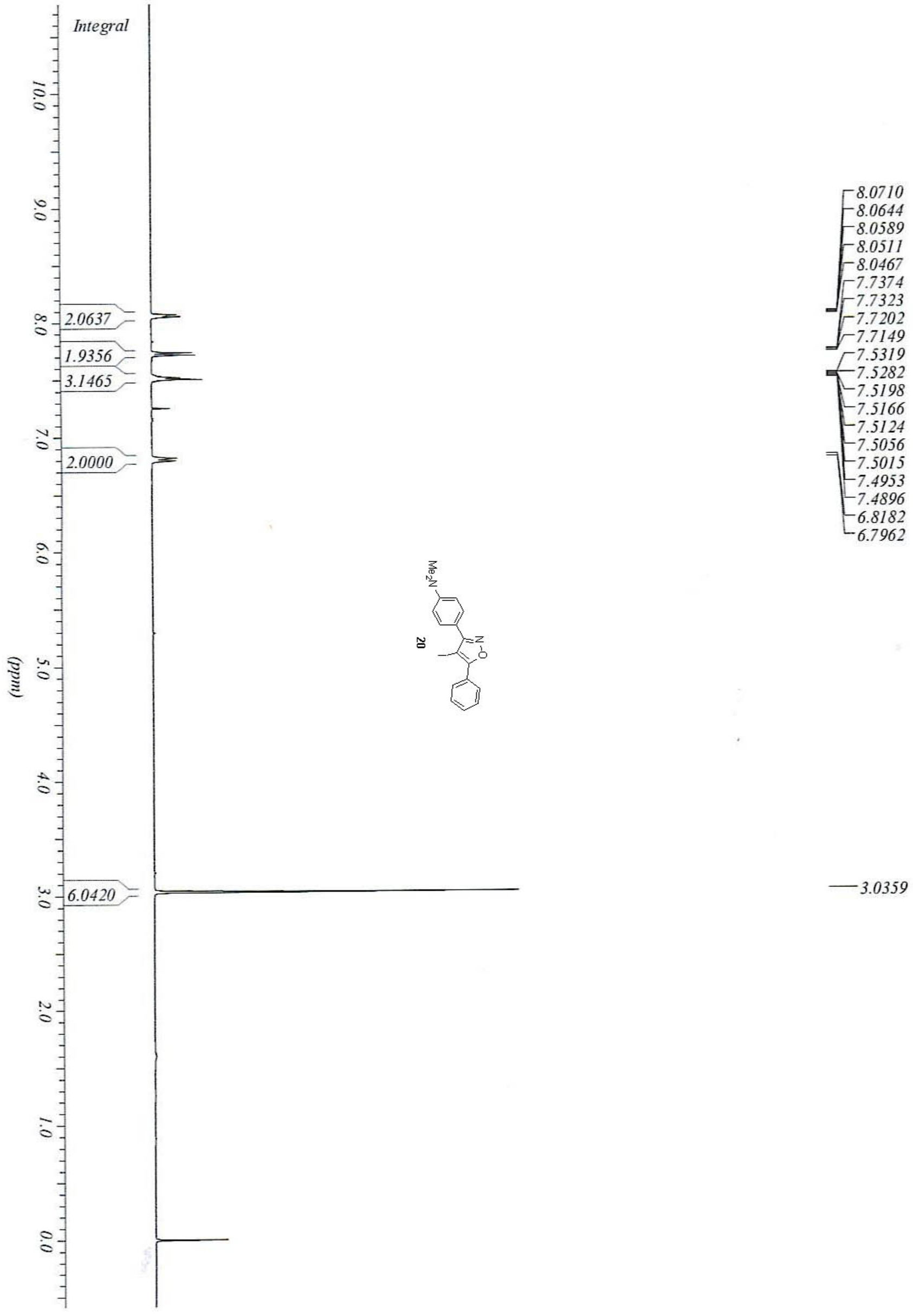
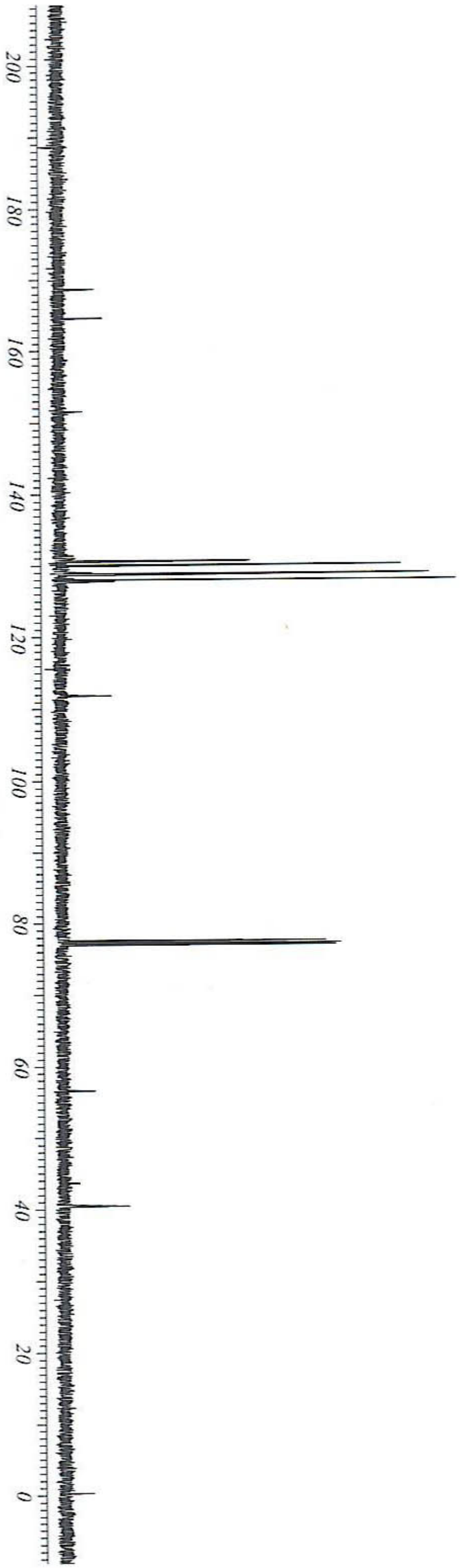
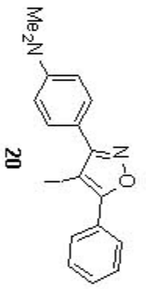


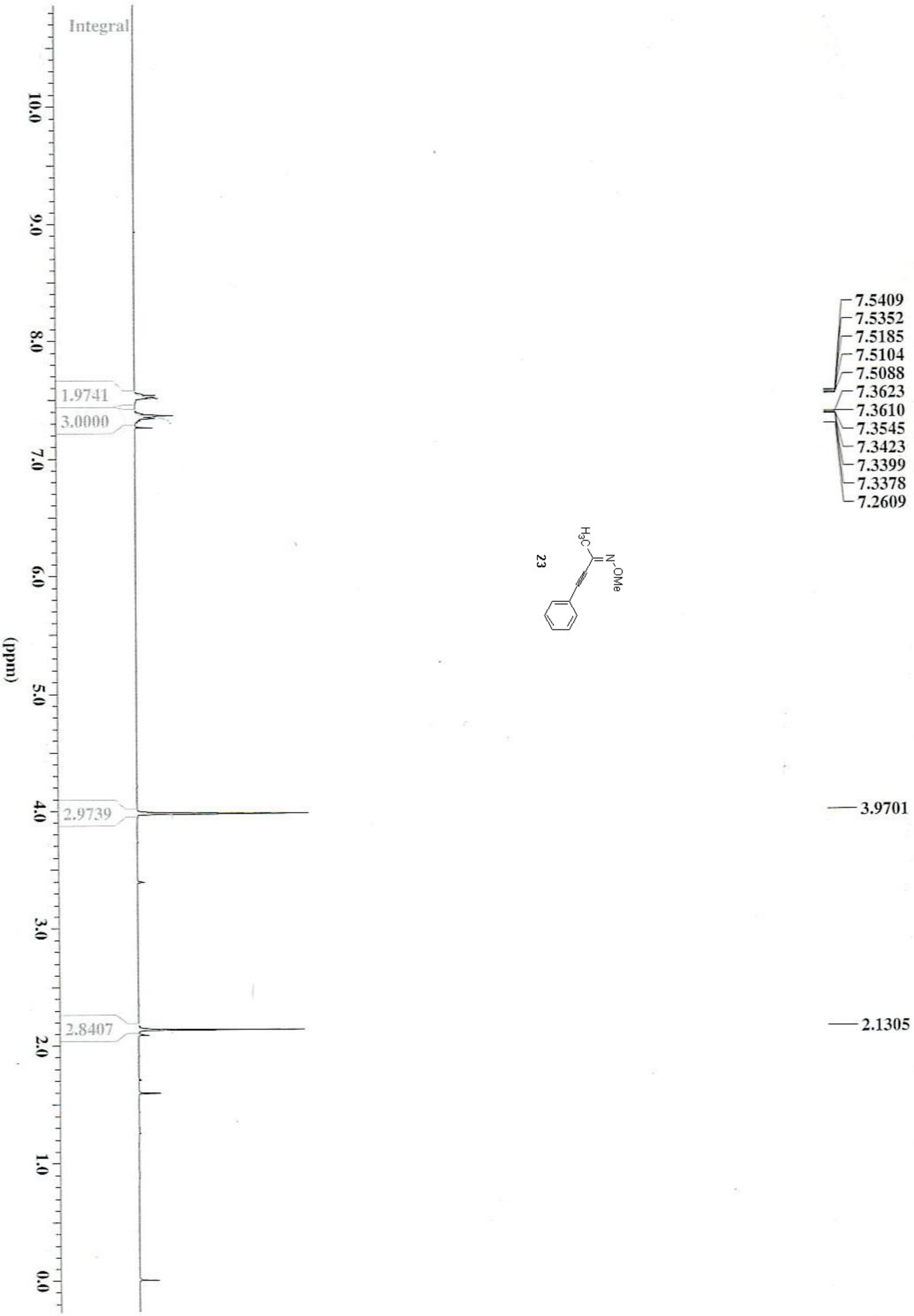

Integral
2.0637
1.9356
3.1465
2.0000
6.0420
3.0359
8.0710
8.0644
8.0589
8.0511
8.0467
7.7374
7.7323
7.7202
7.7149
7.5319
7.5282
7.5198
7.5166
7.5124
7.5056
7.5015
7.4953
7.4896
6.8182
6.7962
Me2N
20
(ppm)



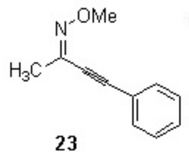


20

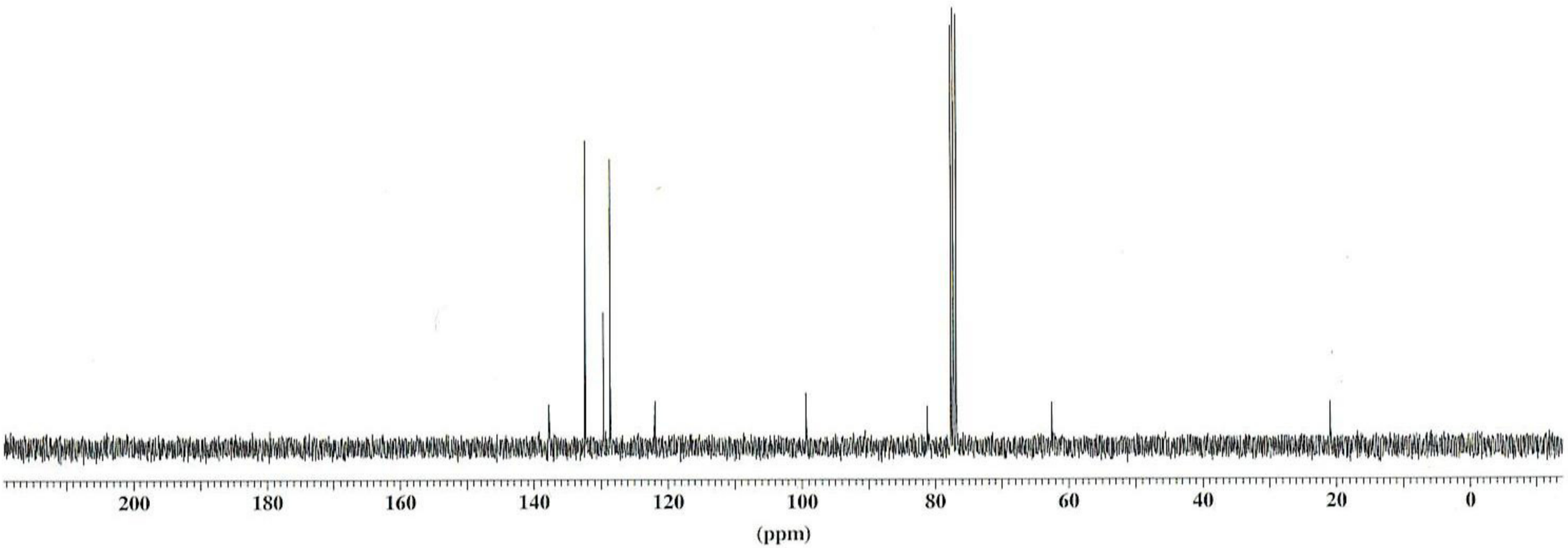
168.6787
164.5768
151.5316
130.6655
130.0134
128.9291
128.8381
127.9776
127.7425
111.8578
56.5875
40.4830

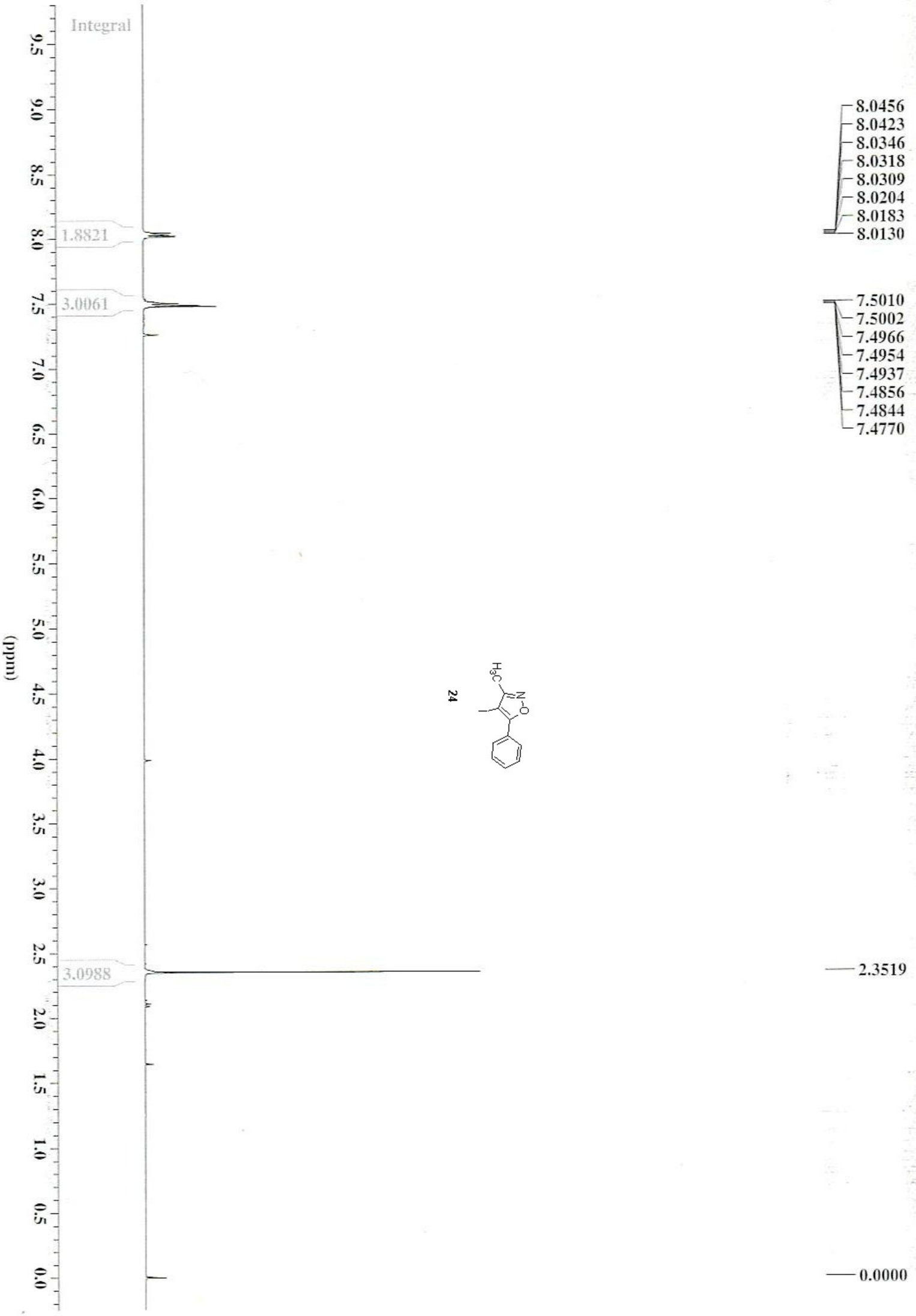

Integral
1.9741
3.0000
2.9739
2.8407
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
7.5409
7.5352
7.5185
7.5104
7.5088
7.3623
7.3610
7.3545
7.3423
7.3399
7.3378
7.2609
3.9701
2.1305
H3C
N
OMe
23

137.7615
132.3158
129.6197
128.5798
121.9232
99.3393
81.1718
77.6708
77.2470
76.8232
62.5199
20.8497



23




Integral
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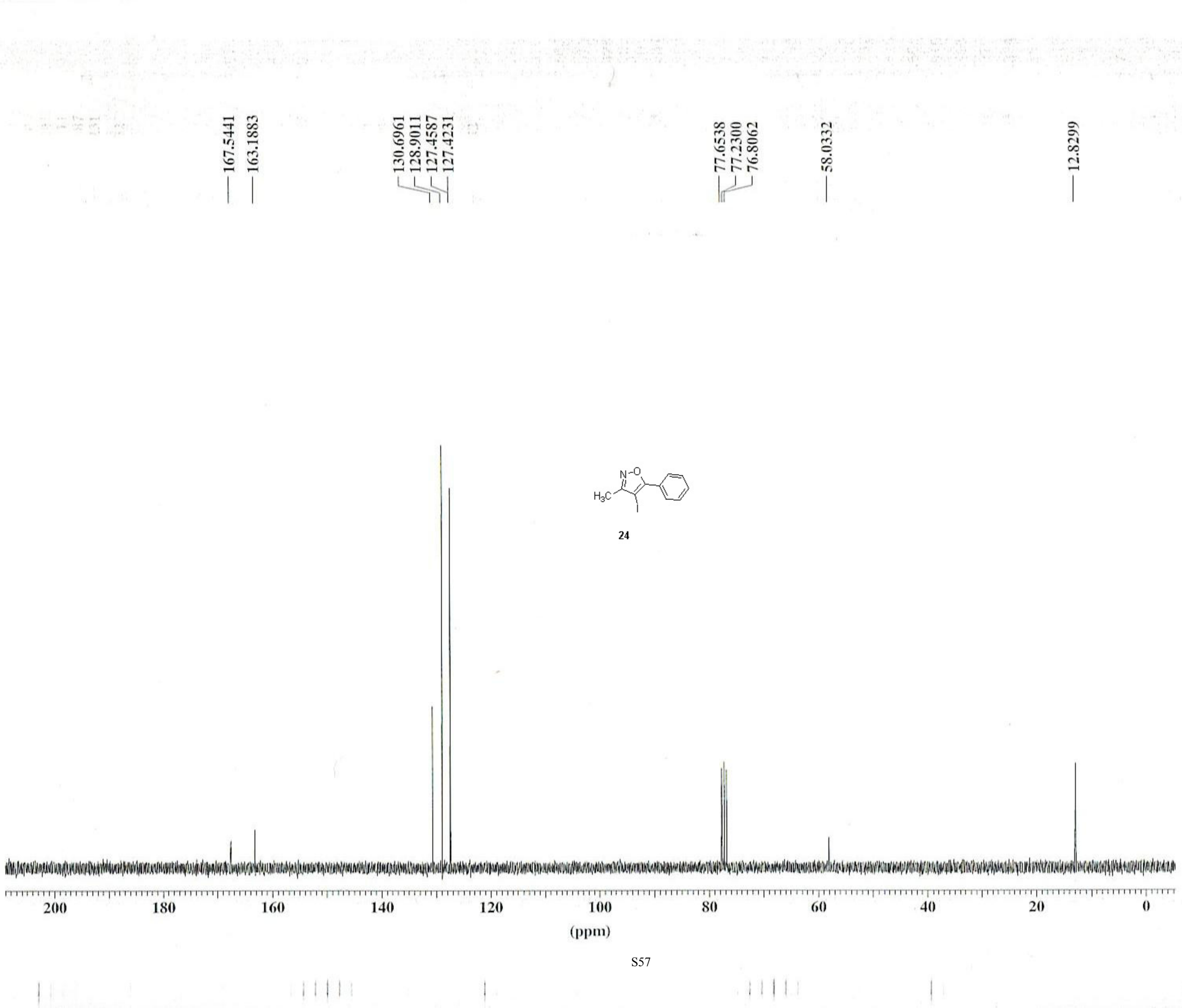
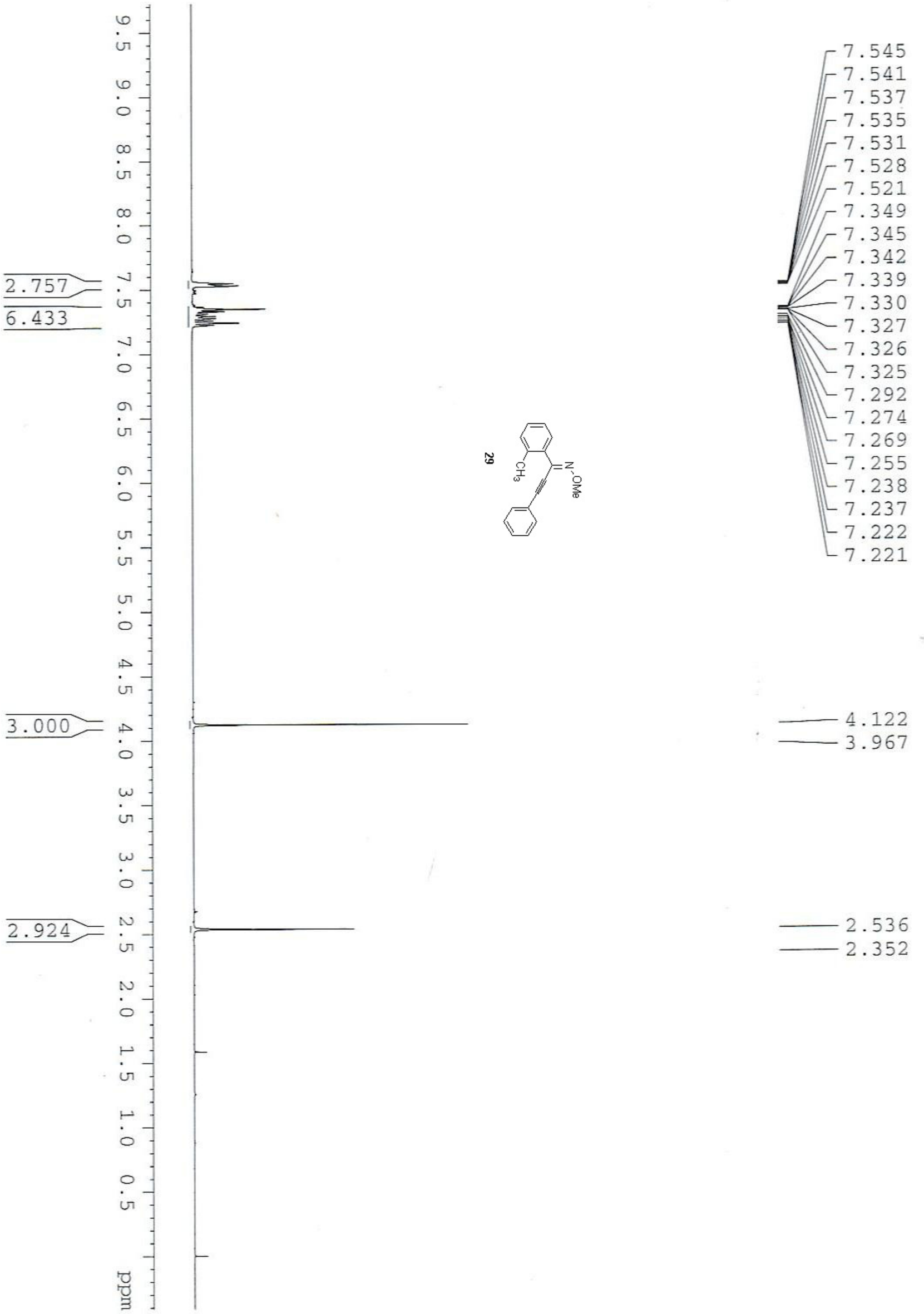
3.0061
3.0988
8.0456
8.0423
8.0346
8.0318
8.0309
8.0204
8.0183
8.0130
7.5010
7.5002
7.4966
7.4954
7.4937
7.4856
7.4844
7.4770
2.3519
0.0000
(ppm)

24


167.5441
163.1883
130.6961
128.9011
127.4587
127.4231
77.6538
77.2300
76.8062
58.0332
12.8299
N
O
H3C
200
180
160
140
120
100
80
60
40
20
0
(ppm)

24


7.545
7.541
7.537
7.535
7.531
7.528
7.521
7.349
7.345
7.342
7.339
7.330
7.327
7.326
7.325
7.292
7.274
7.269
7.255
7.238
7.237
7.222
7.221
N-OMe
CH3
29
4.122
3.967
2.536
2.352
2.757
6.433
3.000
2.924
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

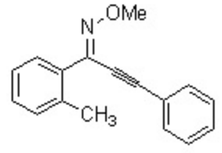
141.105
137.072
133.648
132.321
131.309
129.755
129.694
129.435
128.661
126.225
122.042

101.493

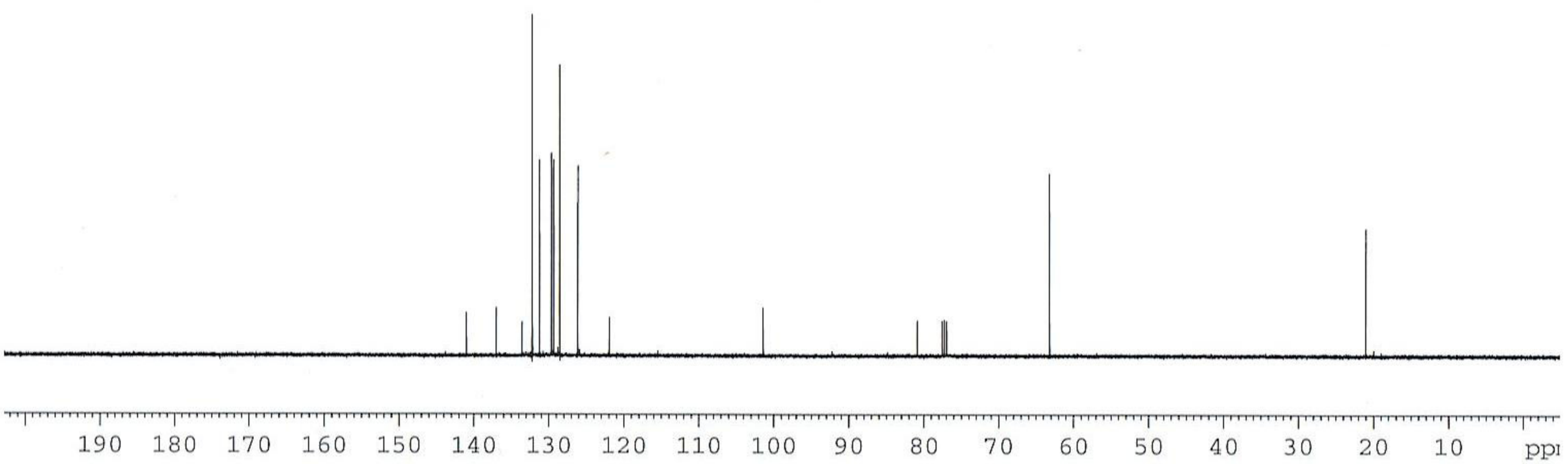
80.977
77.659
77.341
77.023

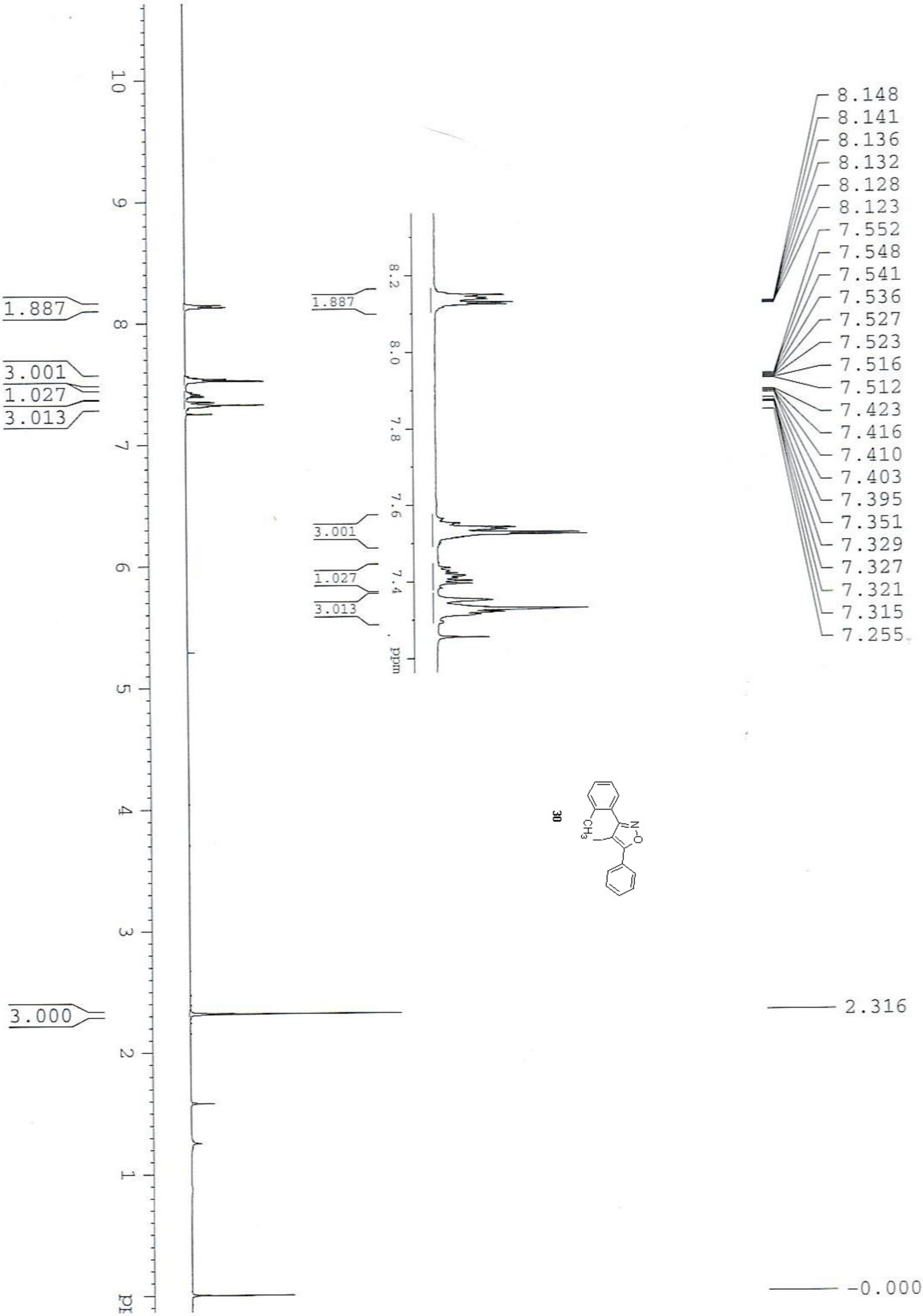
63.288

21.096



29

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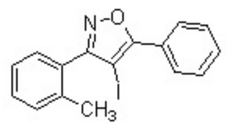
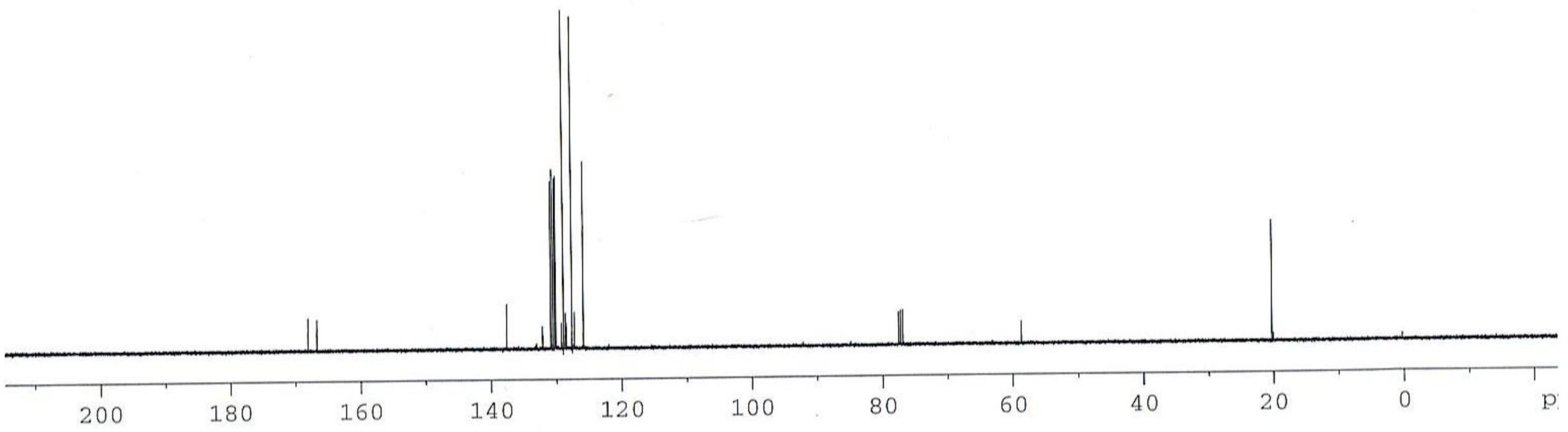
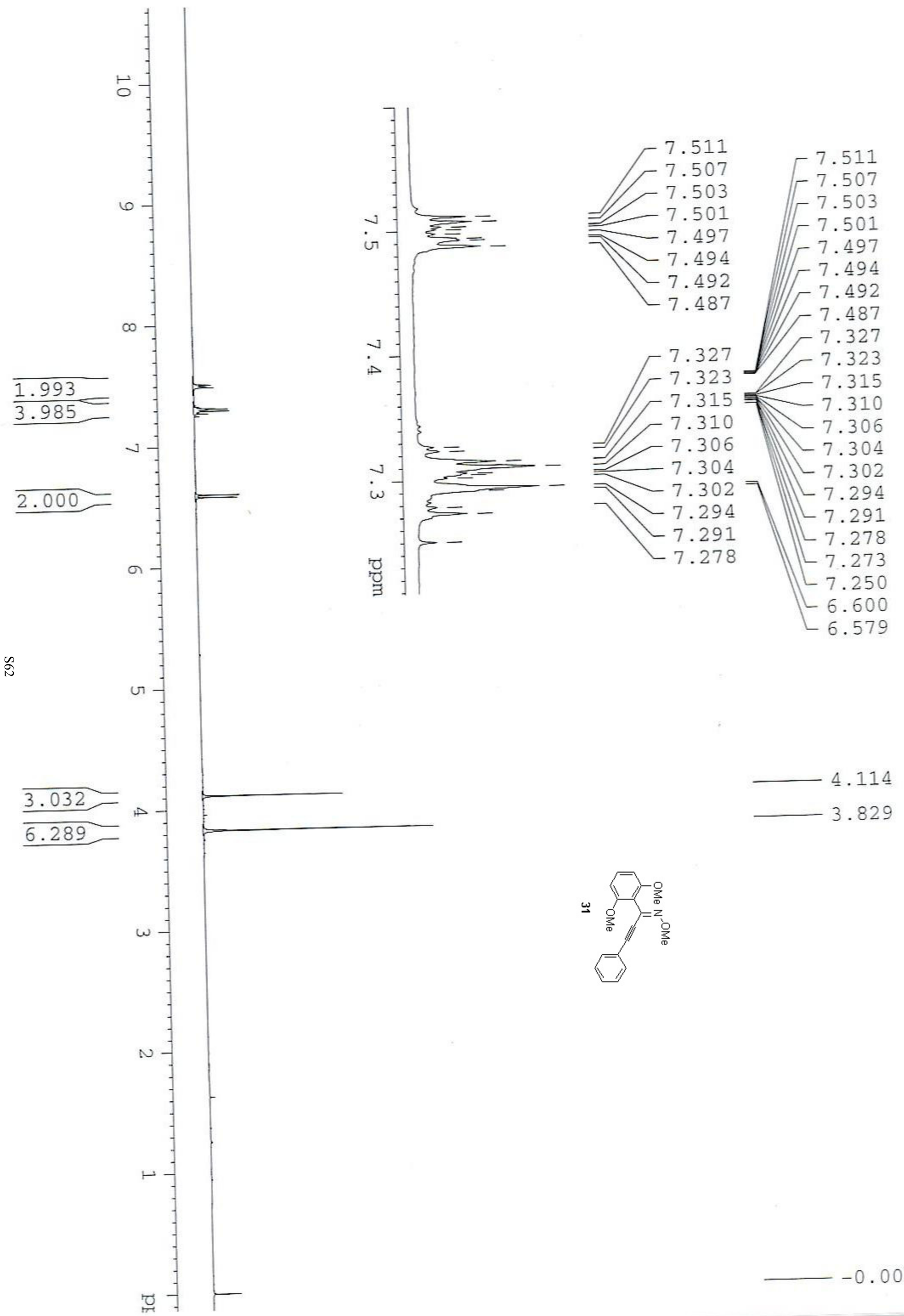
8.141
8.136
8.132
8.128
8.123
7.552
7.548
7.541
7.536
7.527
7.523
7.516
7.512
7.423
7.416
7.410
7.403
7.395
7.351
7.329
7.327
7.321
7.315
7.255
2.316
-0.000
3.000
1.887
3.001
1.027
3.013
ppm
30

168.079
166.749
137.607
130.868
130.582
130.288
130.090
128.940
128.635
127.611
127.300
125.866
77.549
77.231
76.914
58.685
20.224



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2.000
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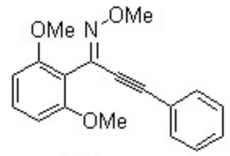
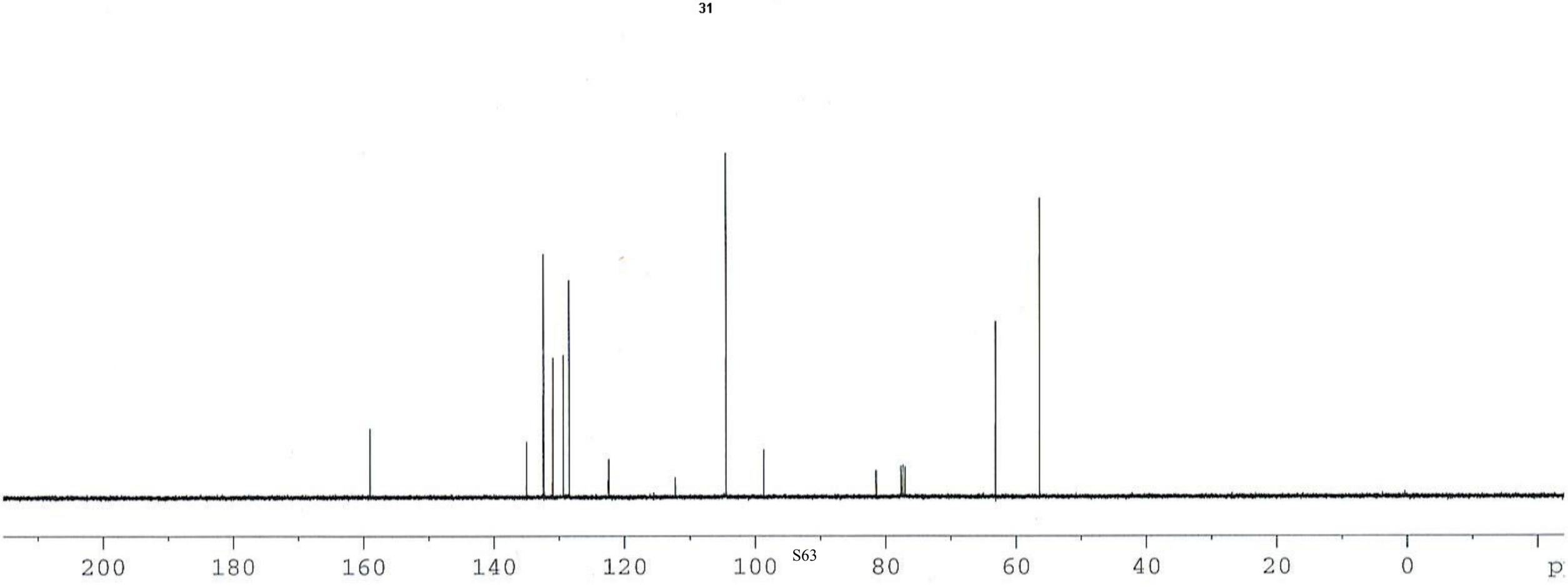
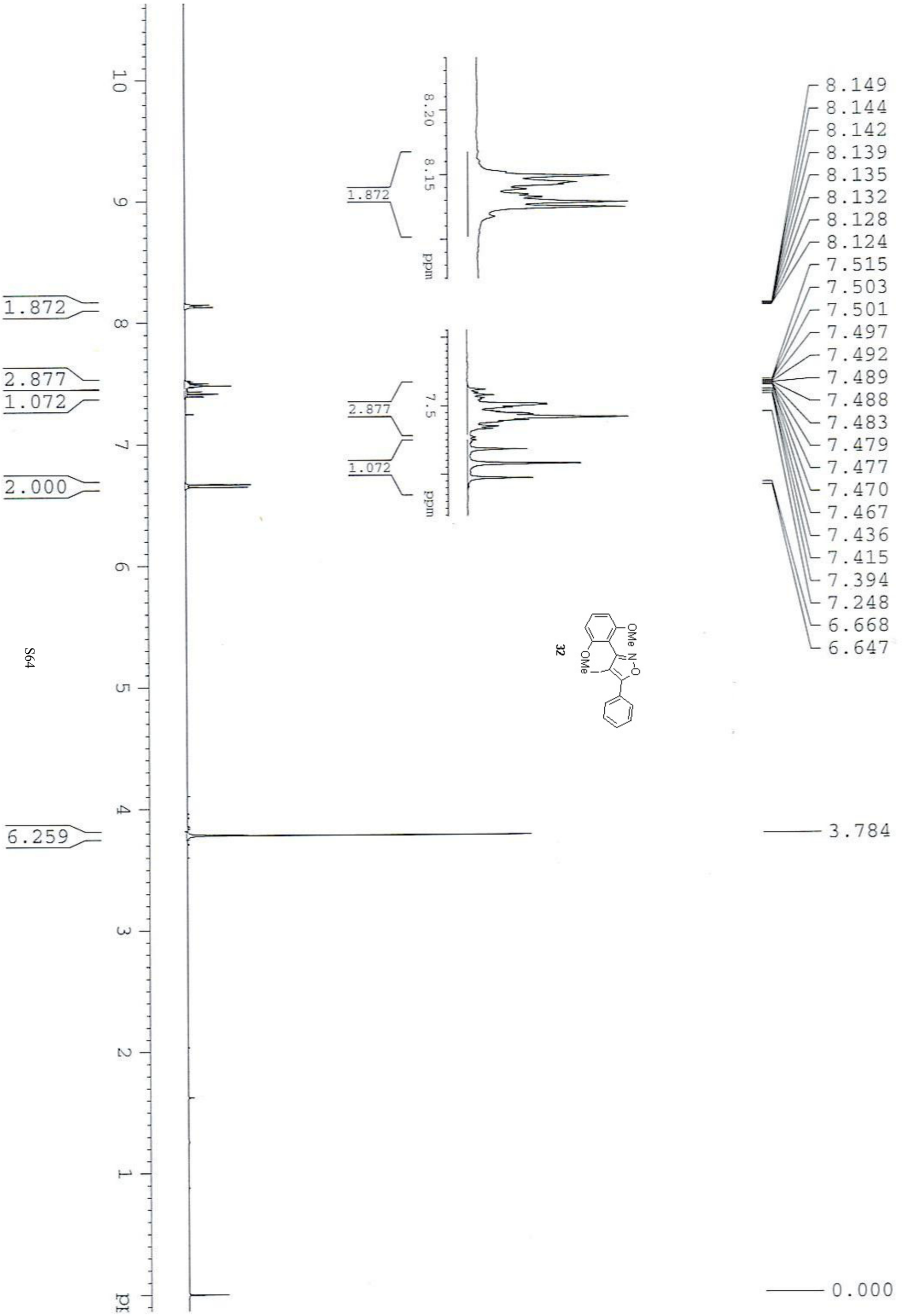
6.289
4.114
3.829
-0.000
7.511
7.507
7.503
7.501
7.497
7.494
7.492
7.487
7.327
7.323
7.315
7.310
7.306
7.304
7.302
7.294
7.291
7.278
7.273
7.250
6.600
6.579
ppm
OMe
OMe
N
OMe
31

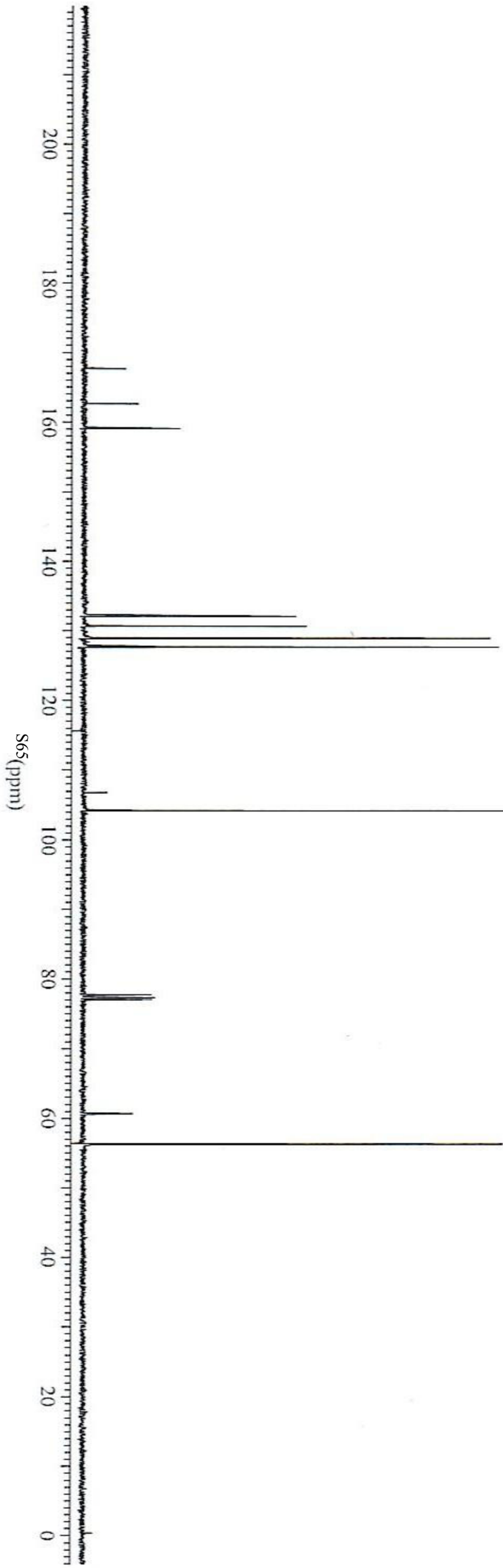
159.026
134.975
132.403
130.972
129.364
128.452
122.430
112.219
104.405
98.615
81.449
77.658
77.342
77.023
63.120
56.356

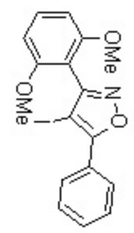


31




8.149
8.144
8.142
8.139
8.135
8.132
8.128
8.124
7.515
7.503
7.501
7.497
7.492
7.489
7.488
7.483
7.479
7.477
7.470
7.467
7.436
7.415
7.394
7.248
6.668
6.647
OMe
OMe
N
O
O
32
1.872
2.877
1.072
2.000
6.259
3.784
0.000
8.20
8.15
ppm
7.5
ppm
1.872
2.877
1.072
10
9
8
7
6
5
4
3
2
1
ppm





32

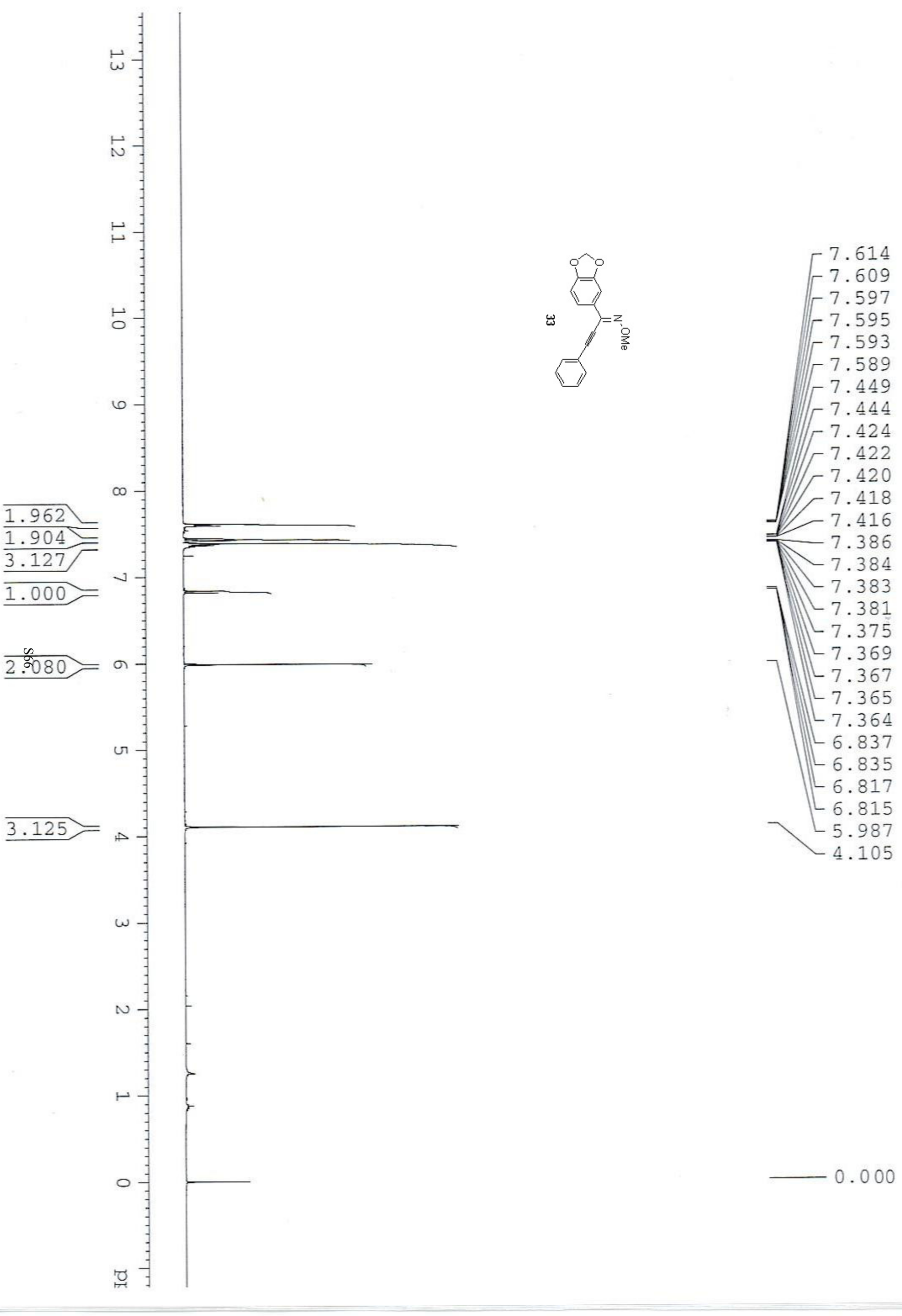
167.5460
162.5646
159.0617

132.0506
130.5721
128.8661
127.7516
127.6151

106.6924
104.1638

77.6417
77.3233
77.0048

60.6769
56.2755


13
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM
1.962
1.904
3.127
1.000
2.080
3.125
33
N
OMe
7.614
7.609
7.597
7.595
7.593
7.589
7.449
7.444
7.424
7.422
7.420
7.418
7.416
7.386
7.384
7.383
7.381
7.375
7.369
7.367
7.365
7.364
6.837
6.835
6.817
6.815
5.987
4.105
0.000

149.272
148.119
139.624
132.371
129.772
128.679
128.090
121.947
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108.292
106.409
101.662
101.126
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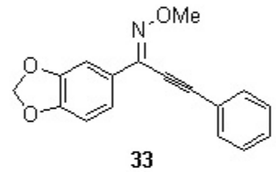
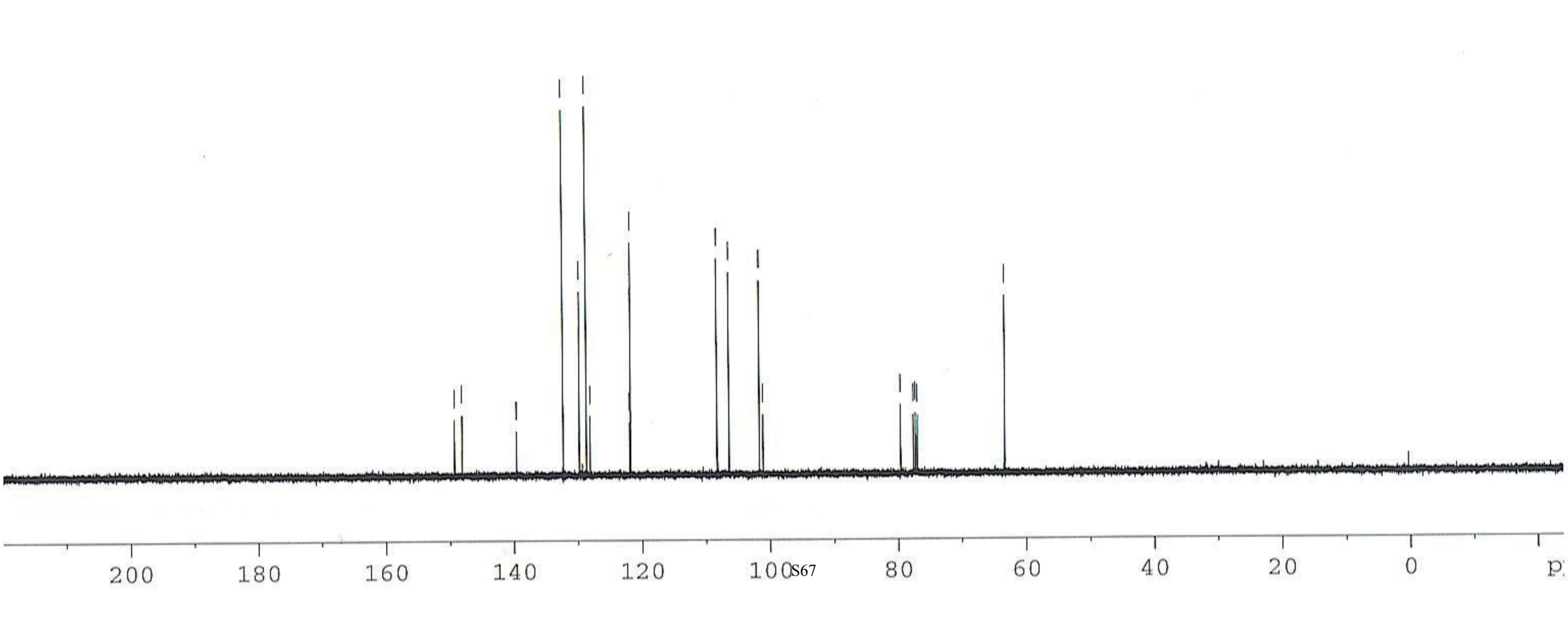
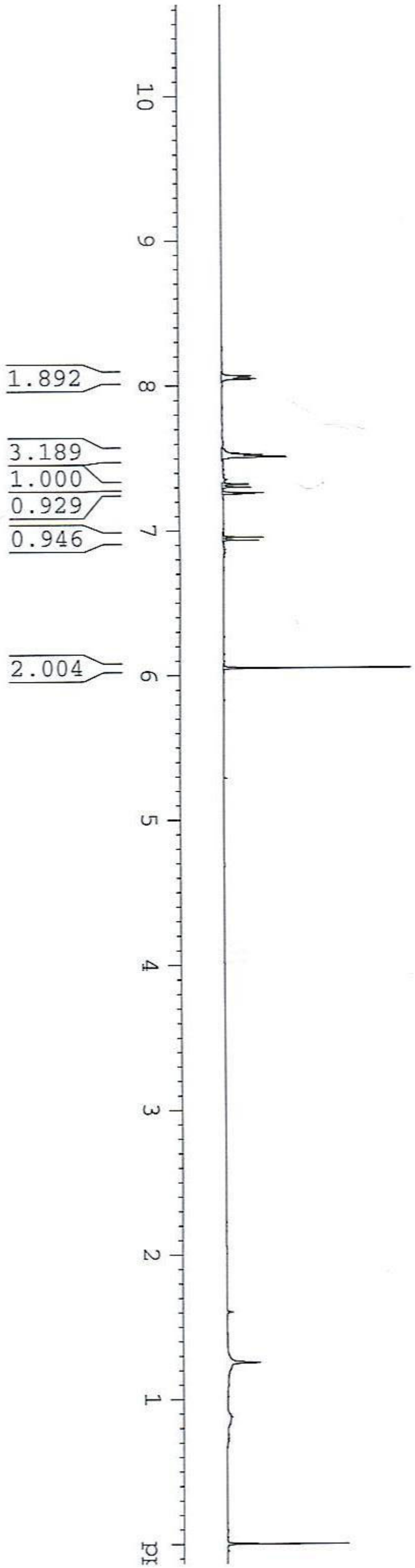
77.623
77.306
76.989
63.311



33




10
9
8
7
6
5
4
3
2
1
pp
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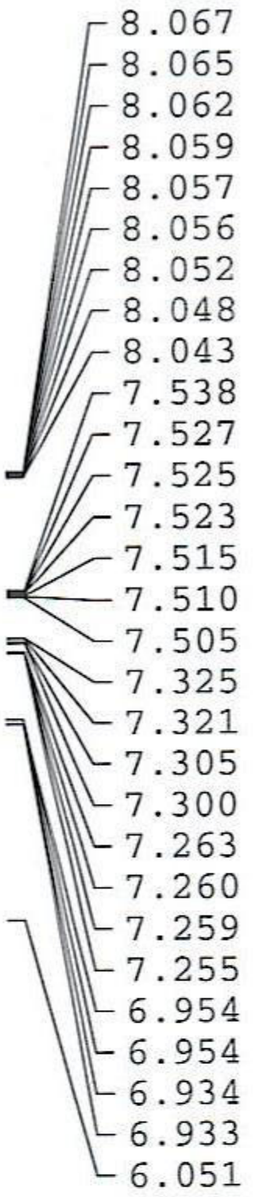
3.189
1.000
0.929
0.946
2.004

34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8.062
8.059
8.057
8.056
8.052
8.048
8.043
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7.527
7.525
7.523
7.515
7.510
7.505
7.325
7.321
7.305
7.300
7.263
7.260
7.259
7.255
6.954
6.954
6.934
6.933
6.051
0.000

169.158
164.457
149.399
147.995
130.940
128.965
128.013
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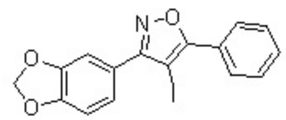
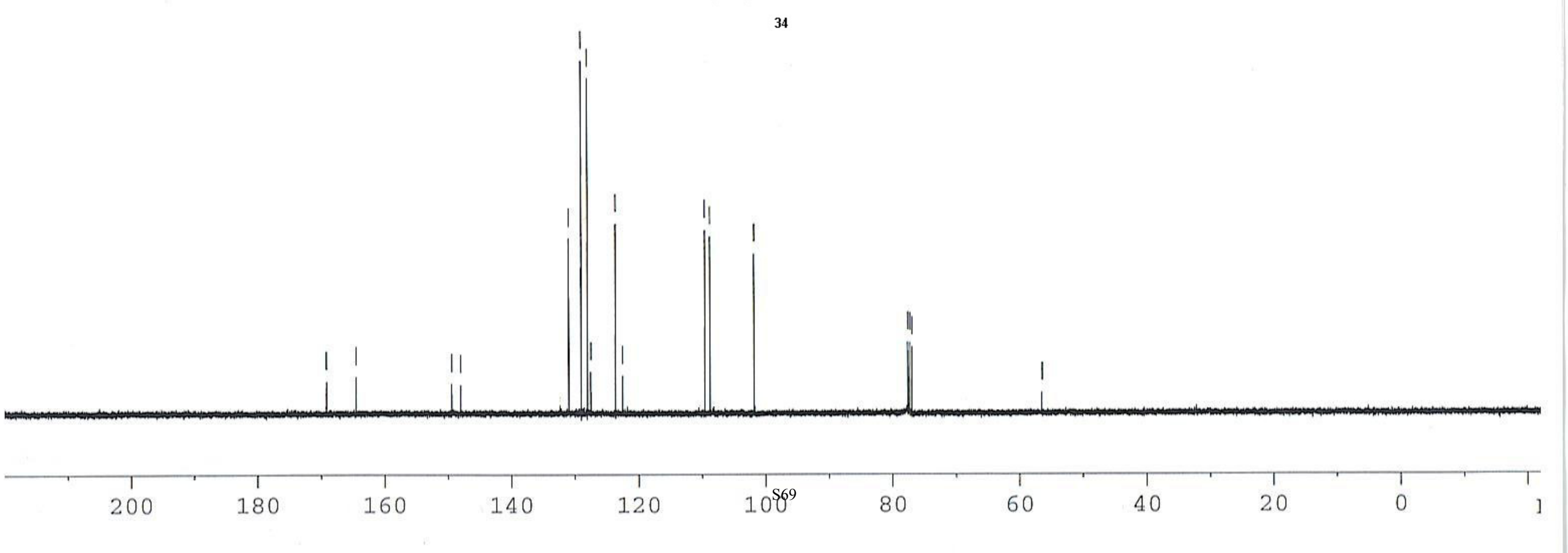
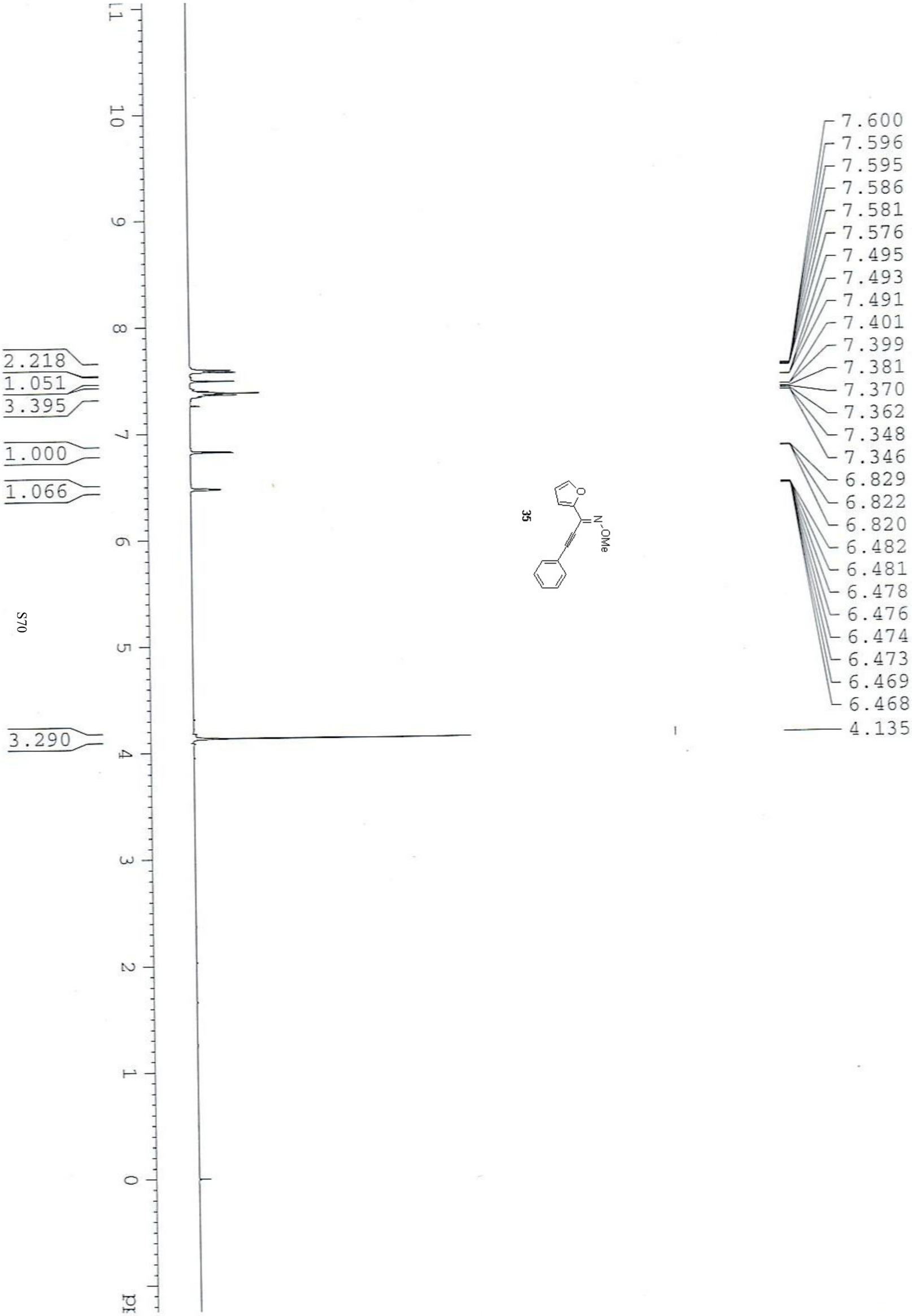
123.616
122.497
109.546
108.724
101.768
77.608
77.289
76.973
56.441

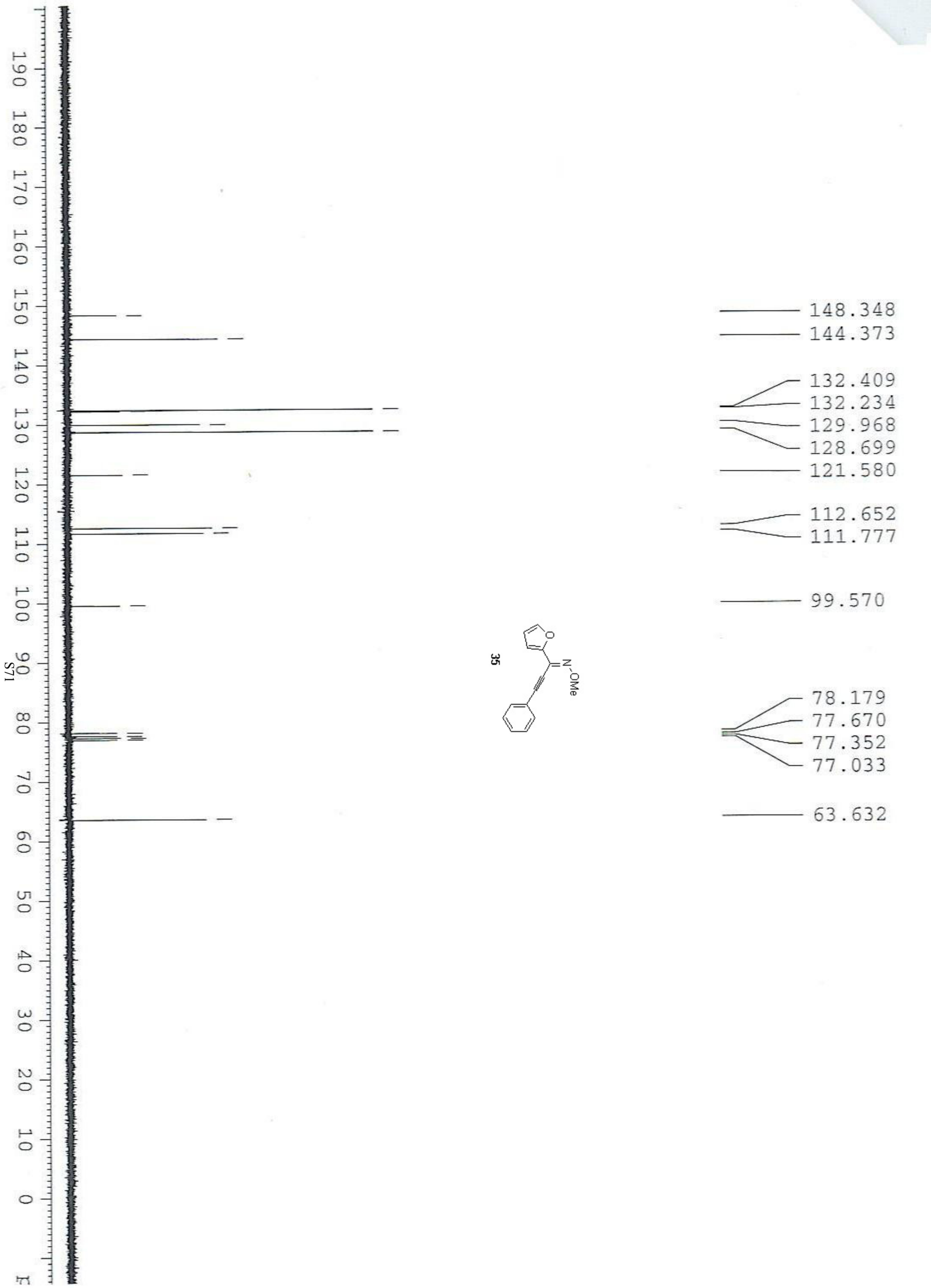


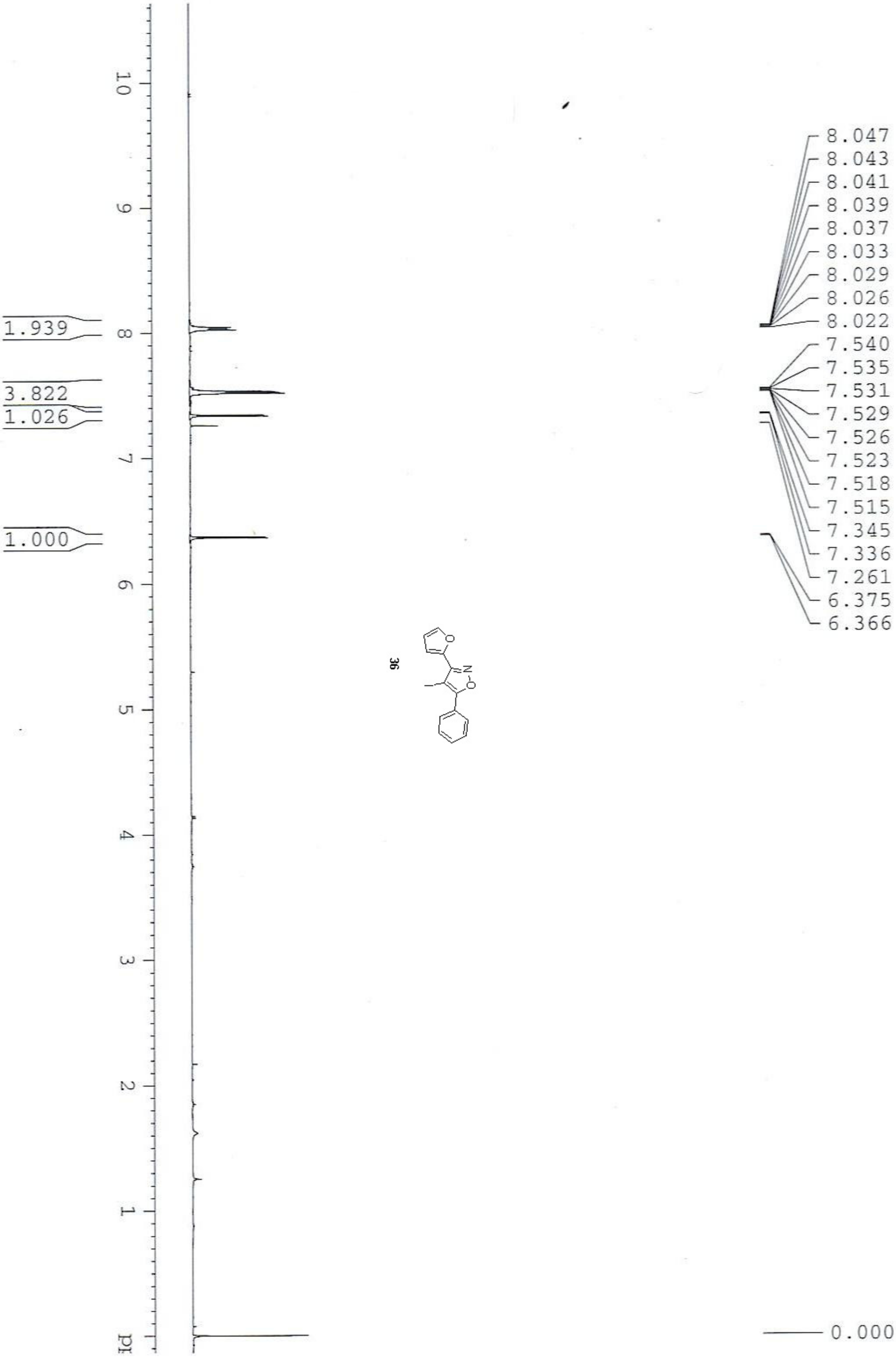
34



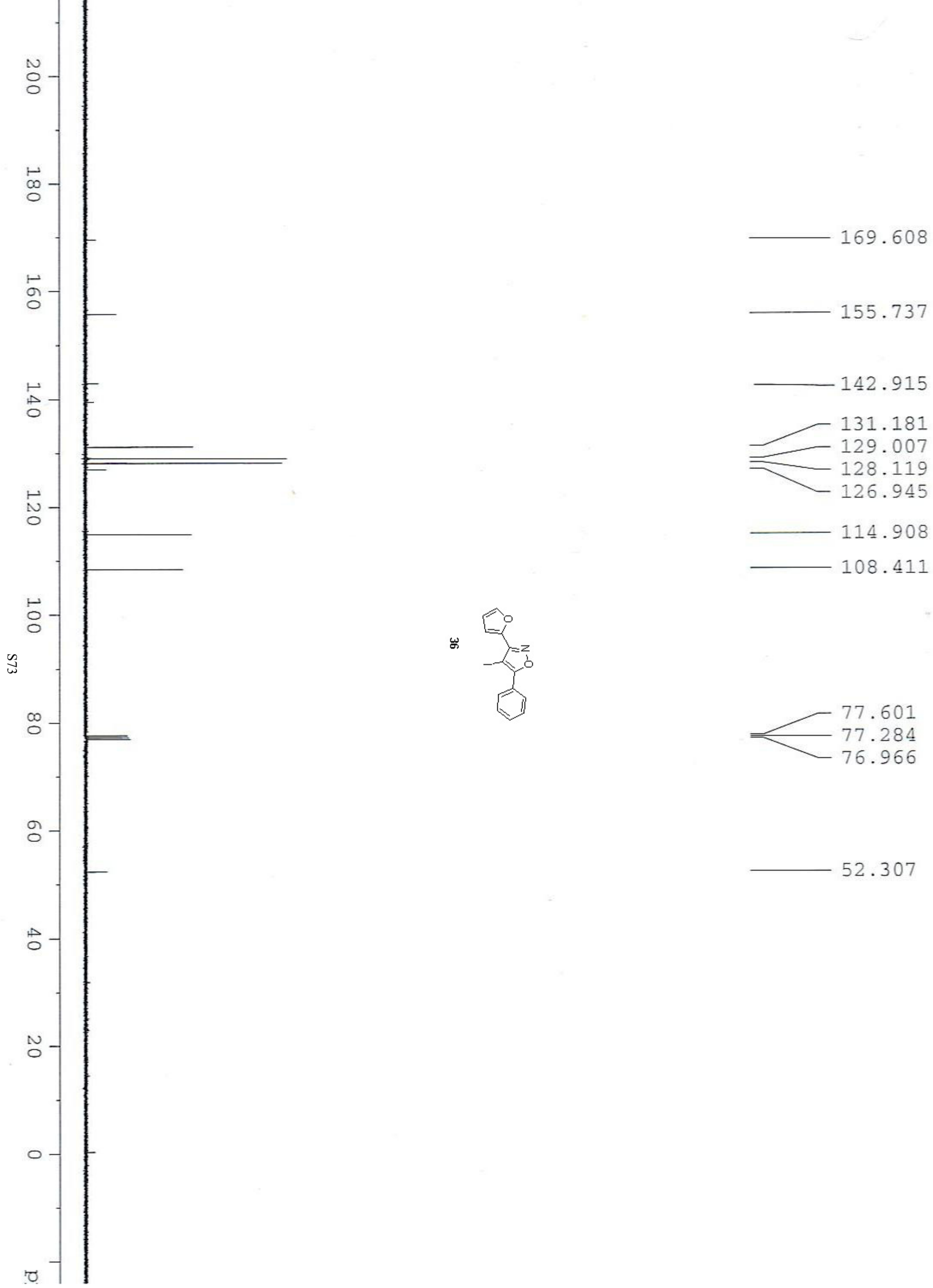

7.600
7.596
7.595
7.586
7.581
7.576
7.495
7.493
7.491
7.401
7.399
7.381
7.370
7.362
7.348
7.346
6.829
6.822
6.820
6.482
6.481
6.478
6.476
6.474
6.473
6.469
6.468
4.135
2.218
1.051
3.395
1.000
1.066
3.290
11
10
9
8
7
6
5
4
3
2
1
0
PPM

35

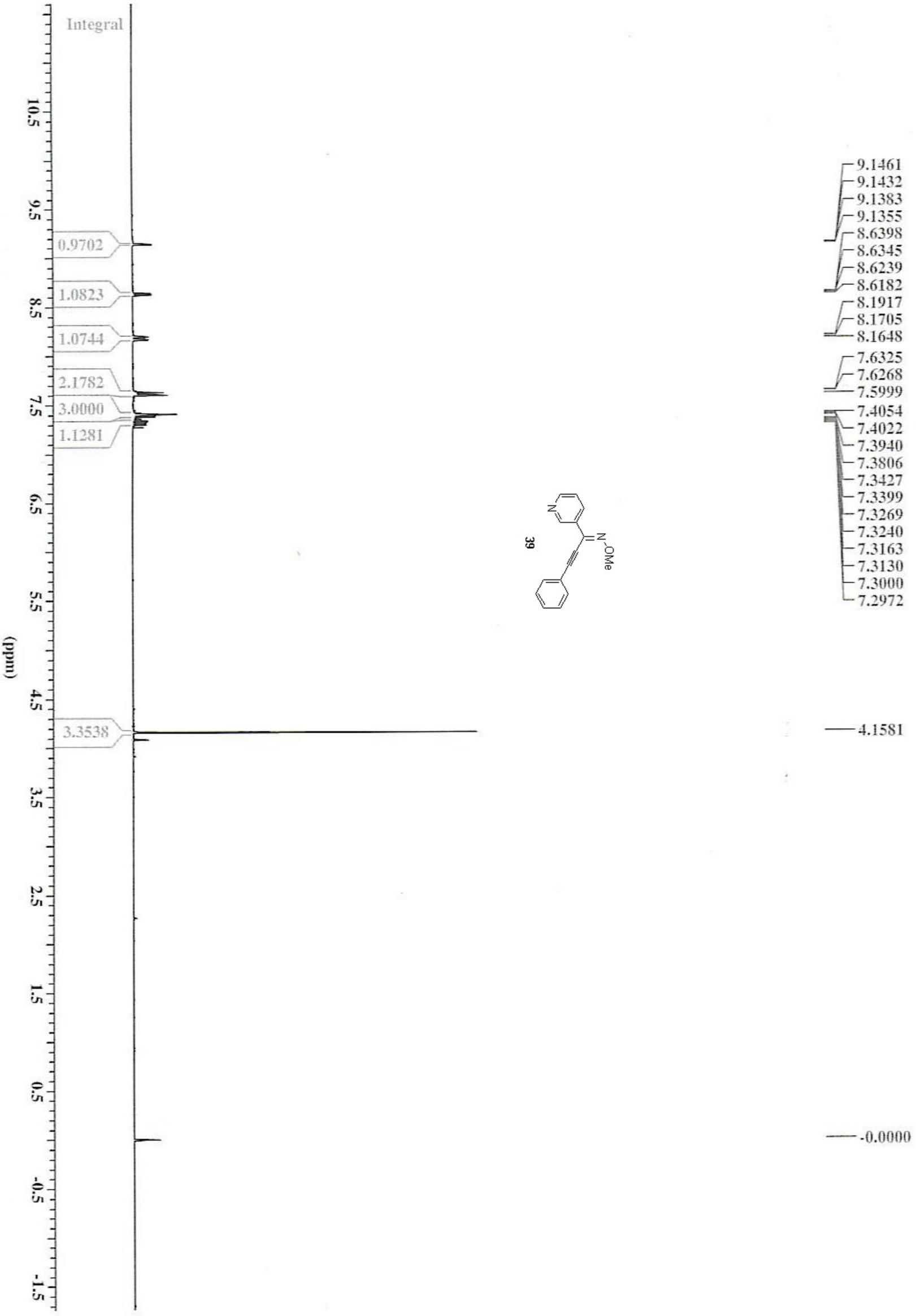

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
148.348
144.373
132.409
132.234
129.968
128.699
121.580
112.652
111.777
99.570
78.179
77.670
77.352
77.033
63.632
35
N
OMe
O

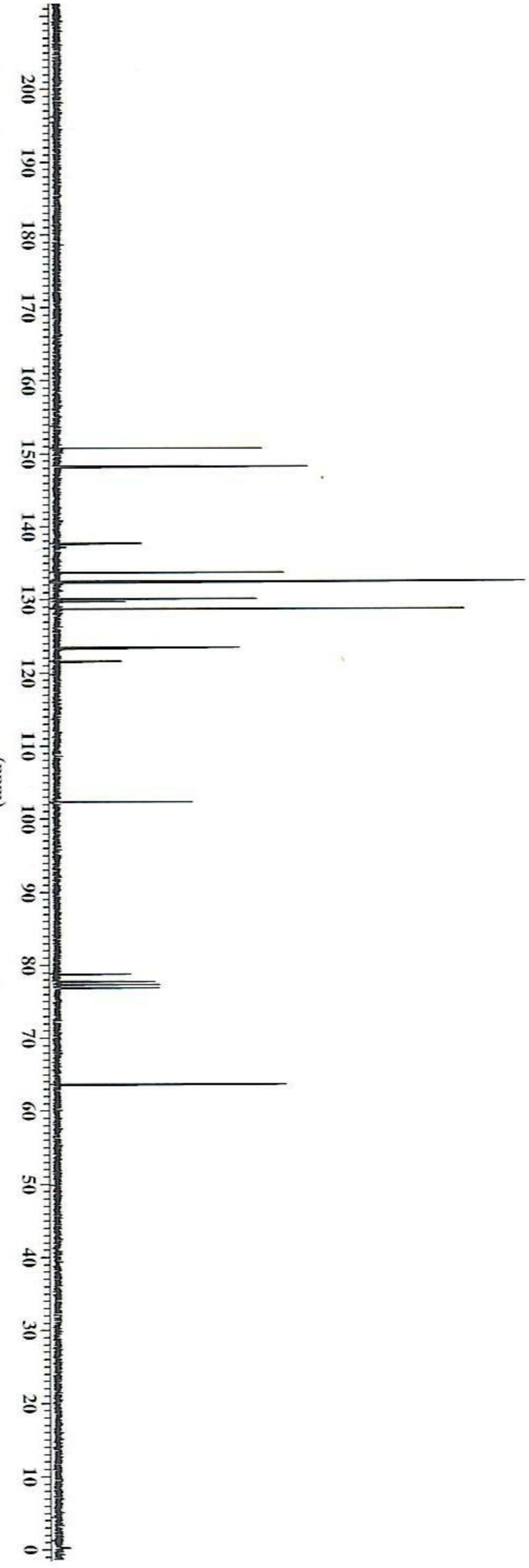

8.047
8.043
8.041
8.039
8.037
8.033
8.029
8.026
8.022
7.540
7.535
7.531
7.529
7.526
7.523
7.518
7.515
7.345
7.336
7.261
6.375
6.366
1.939
3.822
1.026
1.000
0.000
10
9
8
7
6
5
4
3
2
1
ppm

36


169.608
155.737
142.915
131.181
129.007
128.119
126.945
114.908
108.411
77.601
77.284
76.966
52.307
200
180
160
140
120
100
80
60
40
20
0

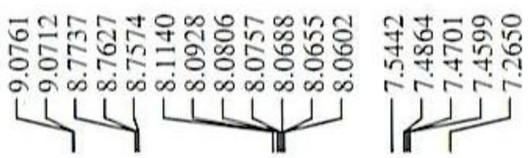
36

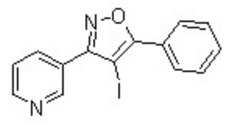

Integral
0.9702
1.0823
1.0744
2.1782
3.0000
1.1281
3.3538
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
(ppm)
9.1461
9.1432
9.1383
9.1355
8.6398
8.6345
8.6239
8.6182
8.1917
8.1705
8.1648
7.6325
7.6268
7.5999
7.4054
7.4022
7.3940
7.3806
7.3427
7.3399
7.3269
7.3240
7.3163
7.3130
7.3000
7.2972
4.1581
-0.0000
N
N
OMe
39



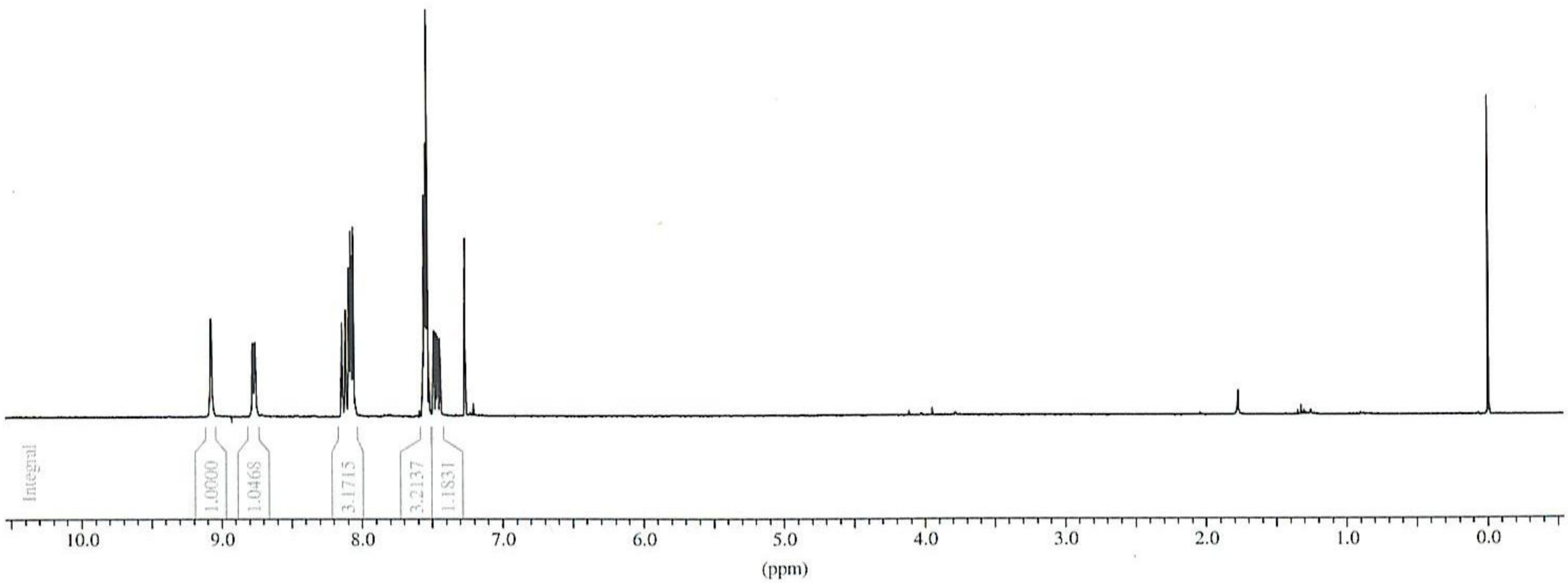
39

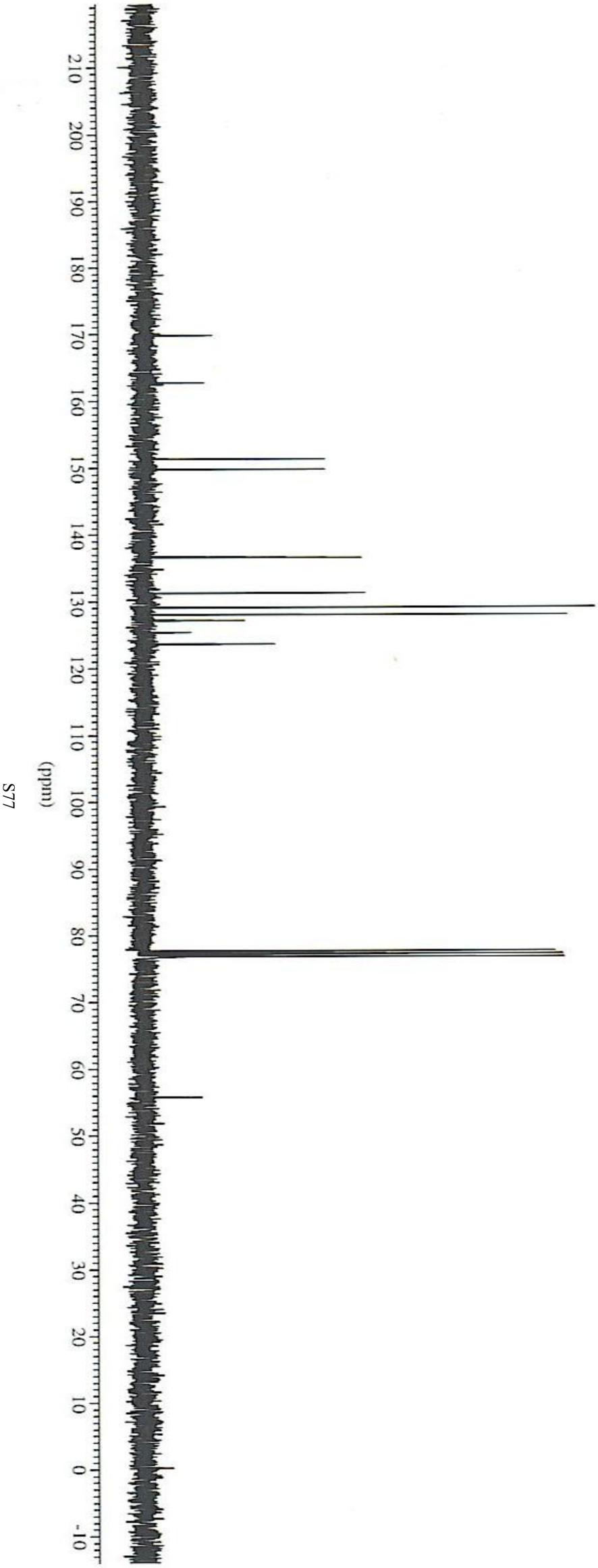
150.7184
148.2645
137.6582
133.6479
132.4227
130.0507
129.7123
128.7400
123.4084
121.5635
102.2919
78.7393
63.6311

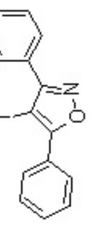

9.0761
9.0712
8.7737
8.7627
8.7574
8.1140
8.0928
8.0806
8.0757
8.0688
8.0655
8.0602
7.5442
7.4864
7.4701
7.4599
7.2650


N
O
N
I

40


Integral
1.0000
1.0468
3.1715
3.2137
1.1831
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)





40

169.7407

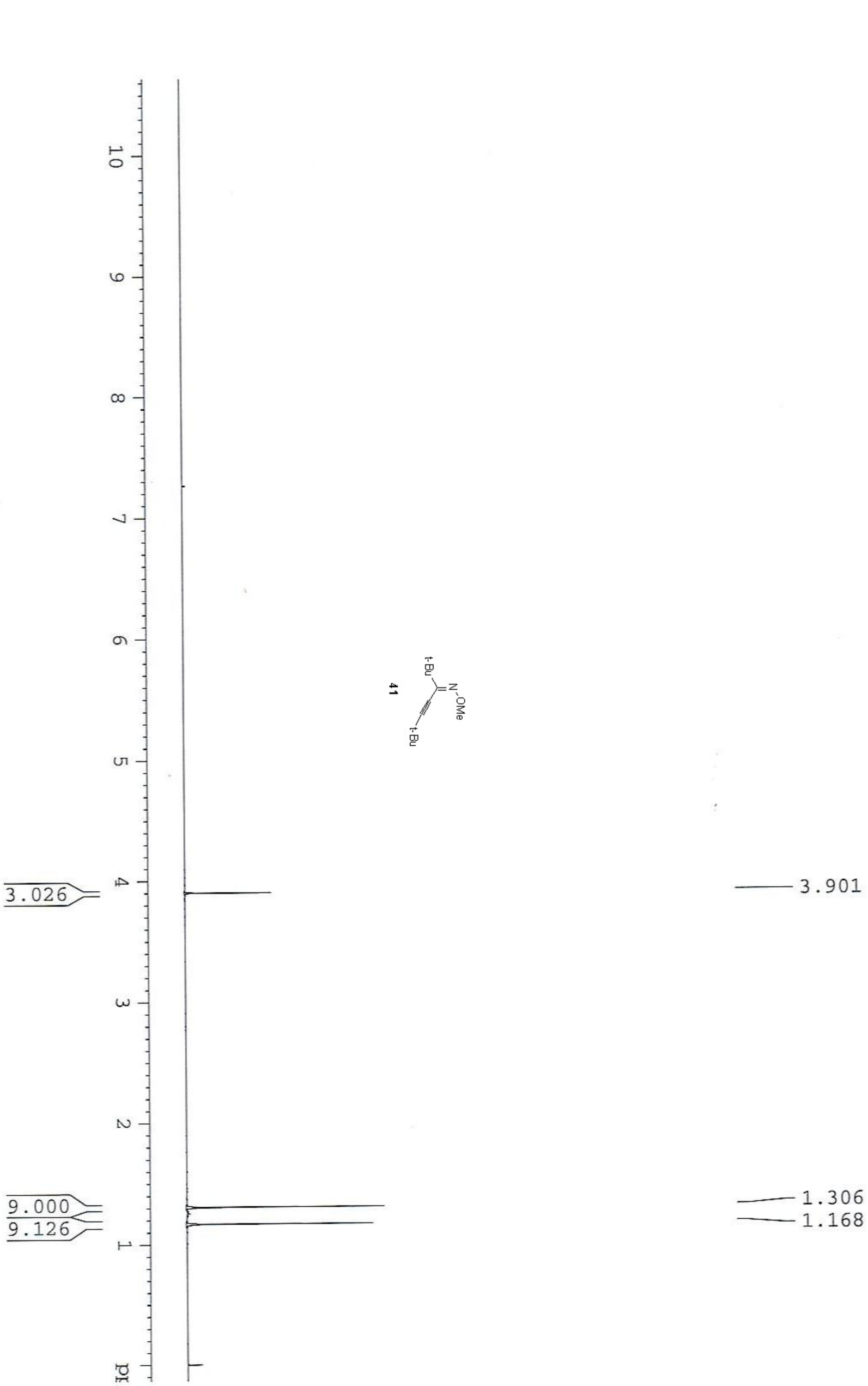
162.6924

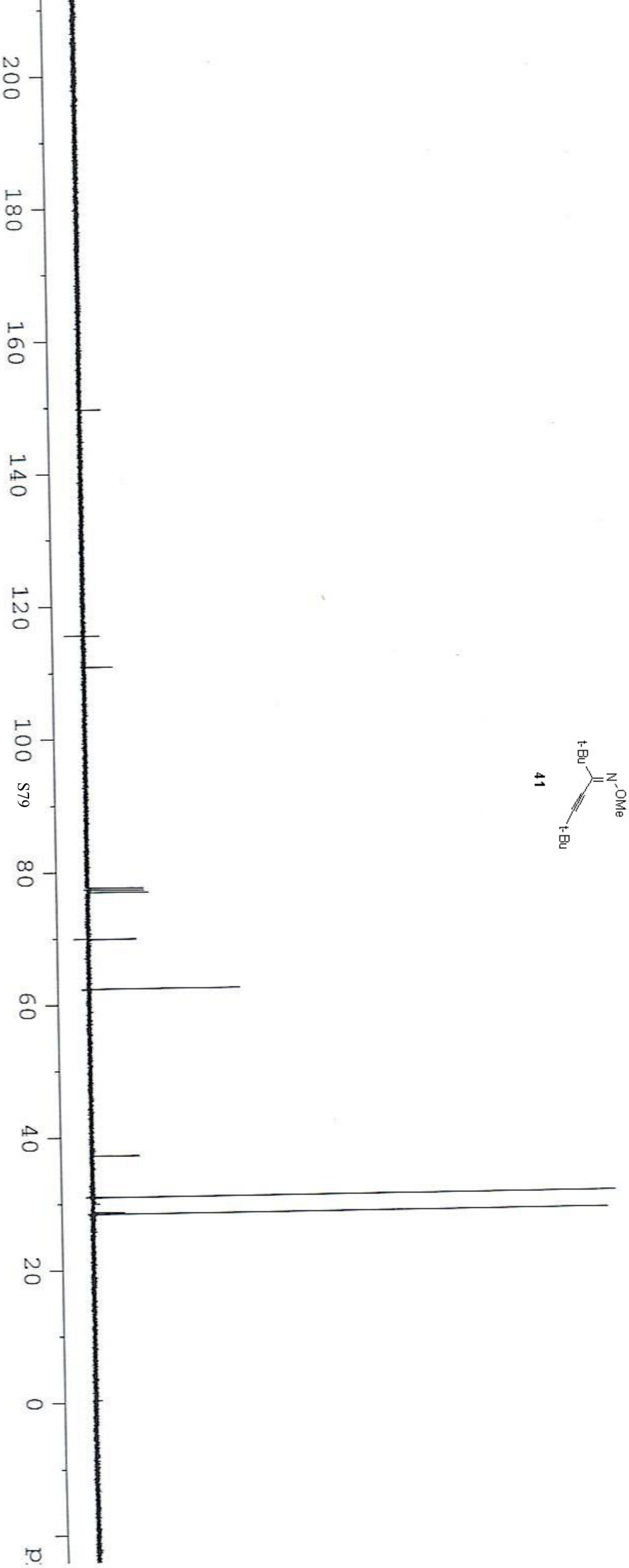
151.3203
149.8316

136.5719
131.1939
129.0641
127.9743
127.1409
125.2960
123.5366

77.6815
77.2577
76.8338

55.7708


41
t-Bu
N
OMe
t-Bu
3.026
9.000
9.126
3.901
1.306
1.168
10
9
8
7
6
5
4
3
2
1
ppm



41

149.663

110.869

77.589
77.272
76.955

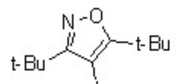
69.878

62.286

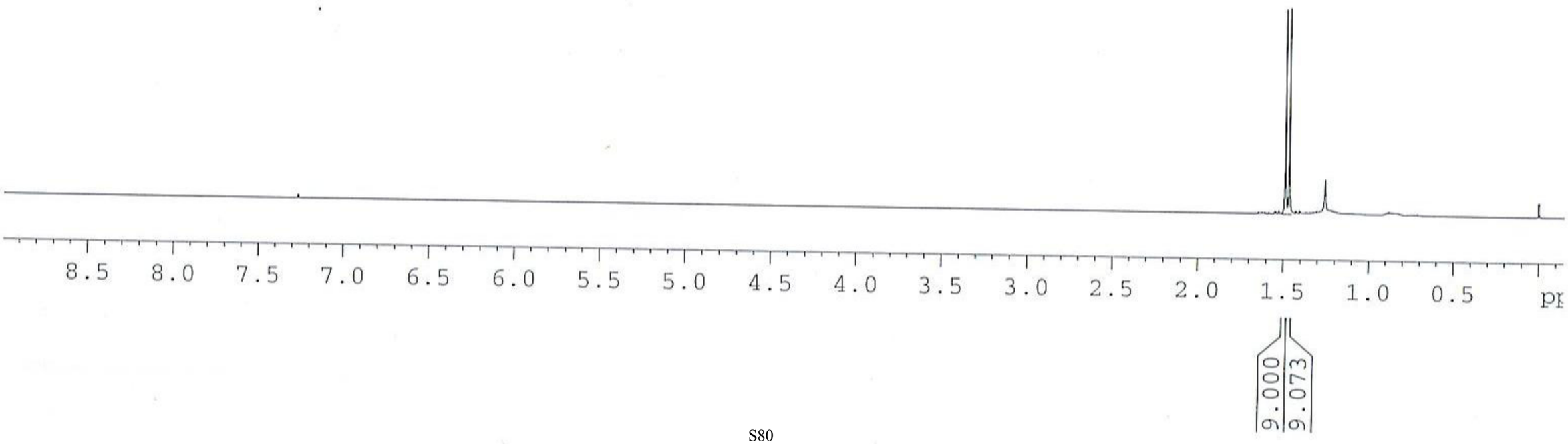
37.142

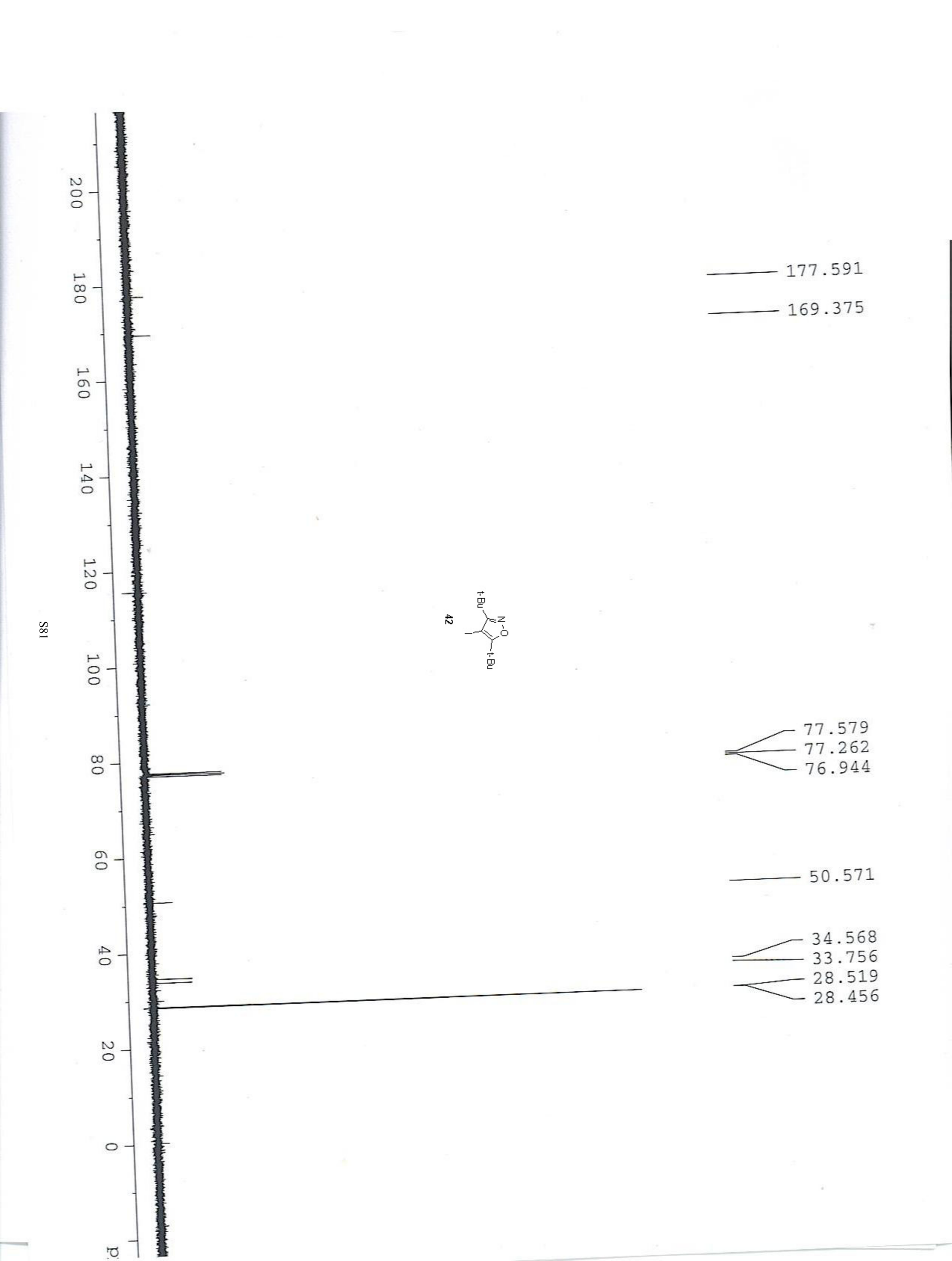
30.898
28.364
28.354

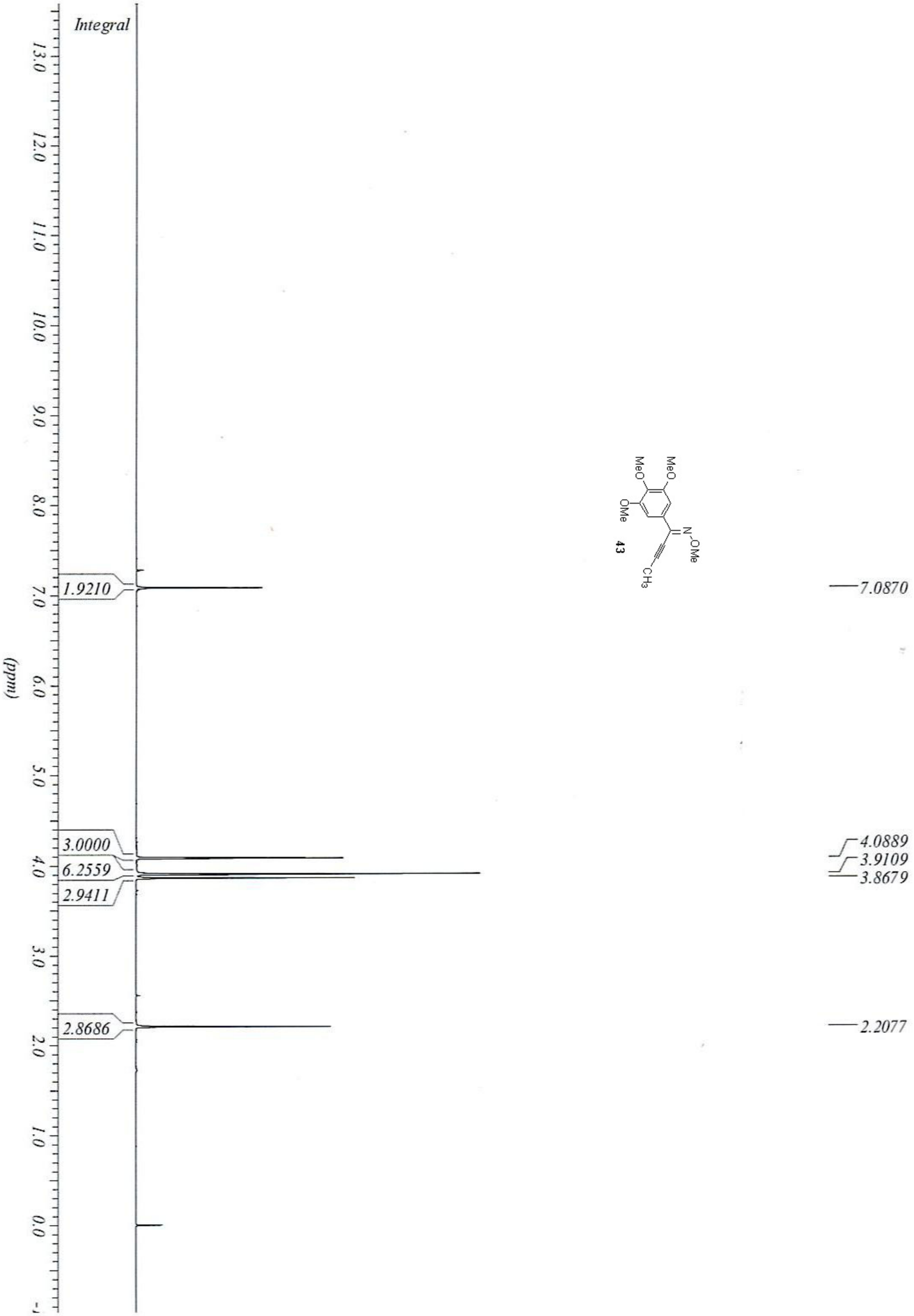
1.488
1.466


N
O
t-Bu
t-Bu

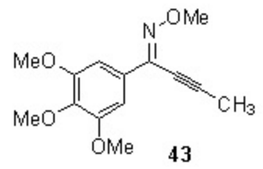
42


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
9.000
9.073

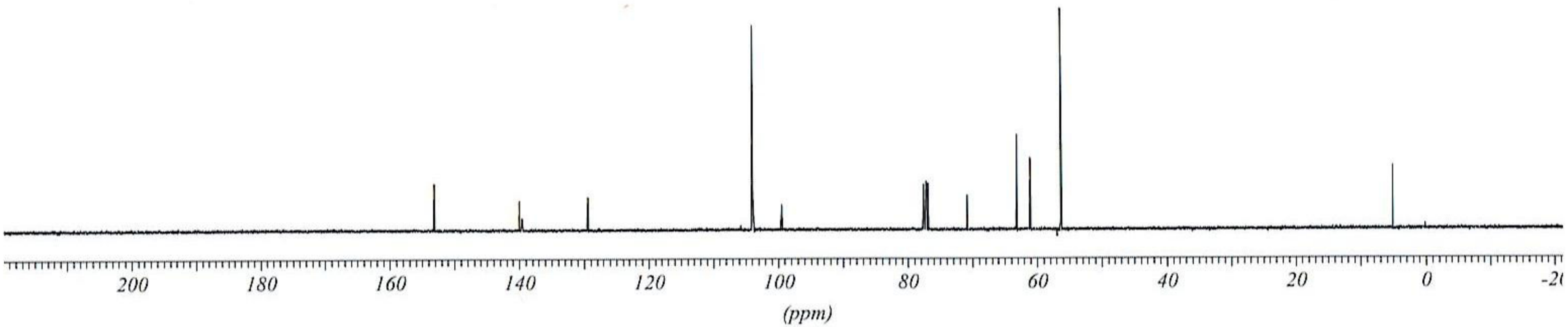

177.591
169.375
77.579
77.262
76.944
50.571
34.568
33.756
28.519
28.456
t-Bu
t-Bu
42
200
180
160
140
120
100
80
60
40
20
0

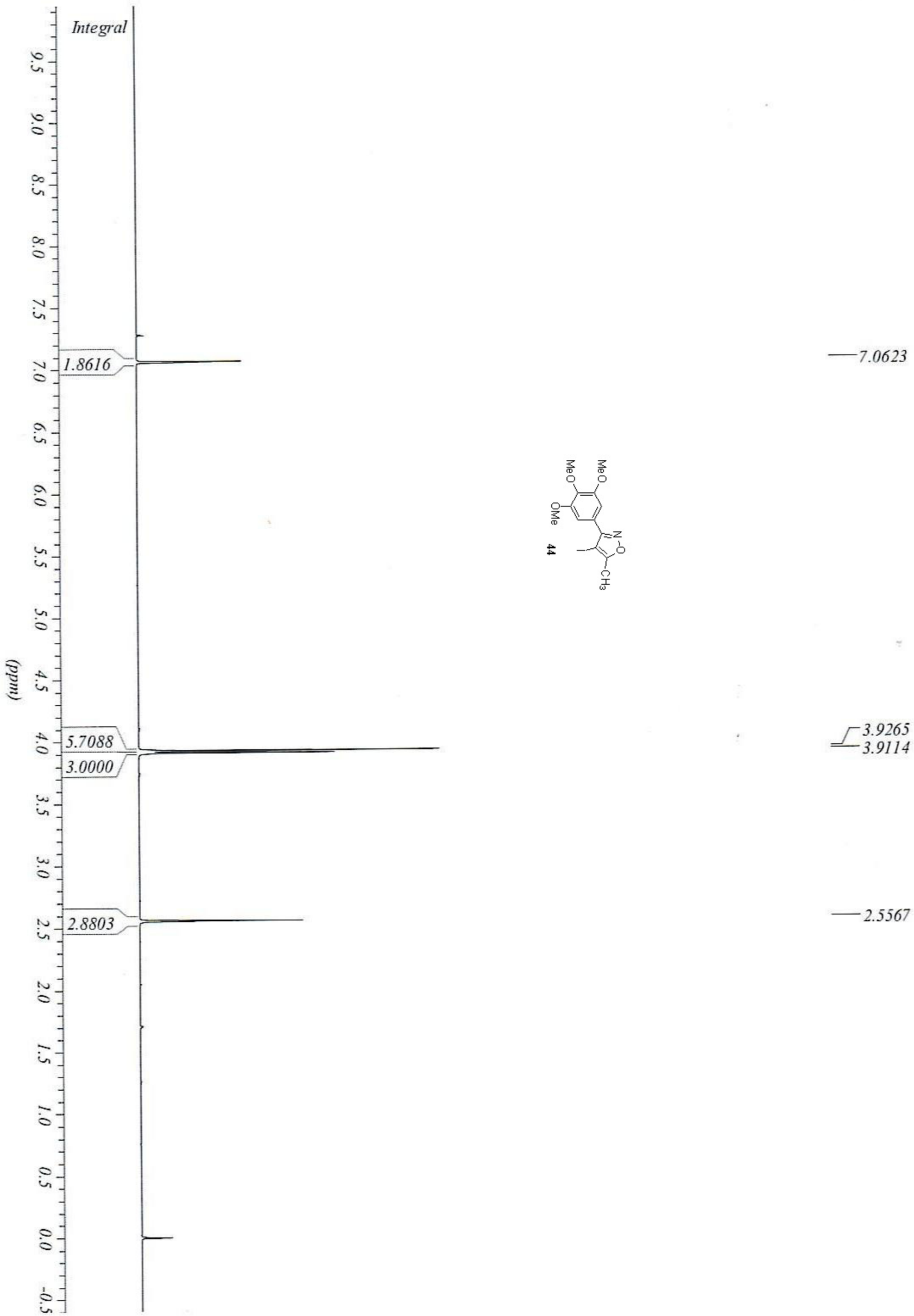

Integral
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
1.9210
3.0000
6.2559
2.9411
2.8686
MeO
MeO
OMe
N
OMe
CH3
43
7.0870
4.0889
3.9109
3.8679
2.2077

153.1390
140.0029
139.5783
129.3992
103.9269
99.4951
70.8420
63.1385
61.0496
56.3259
5.0742



43




Integral
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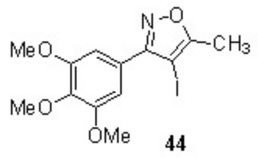
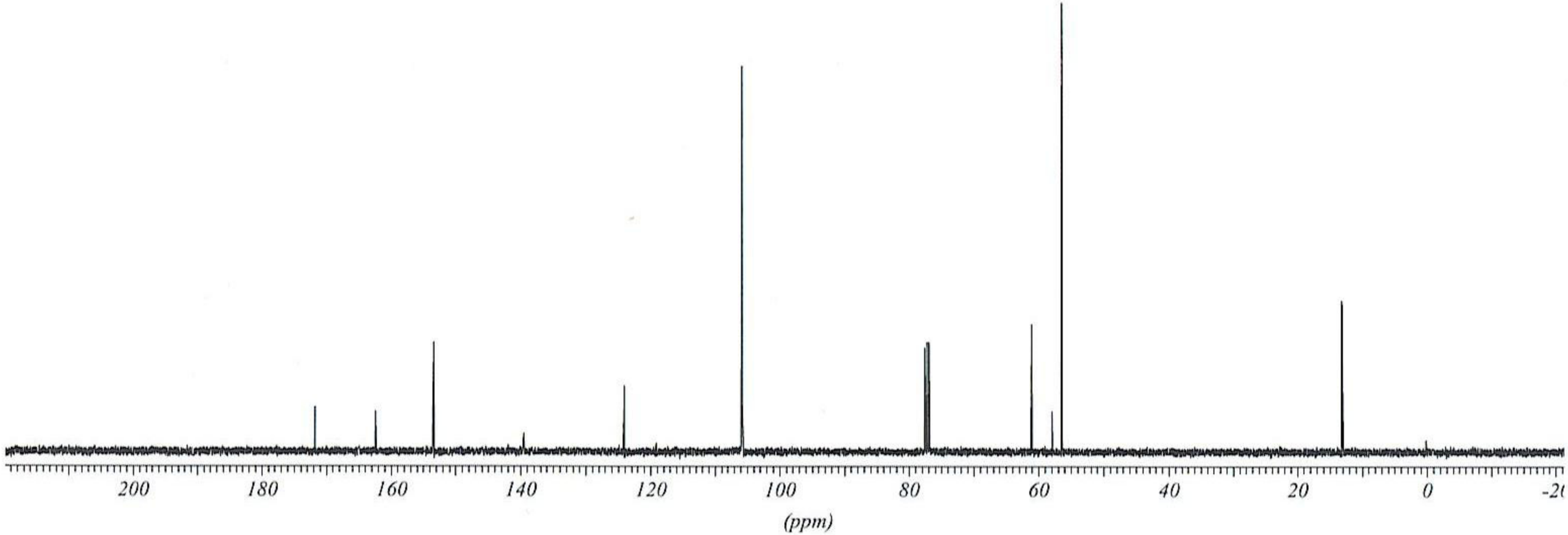
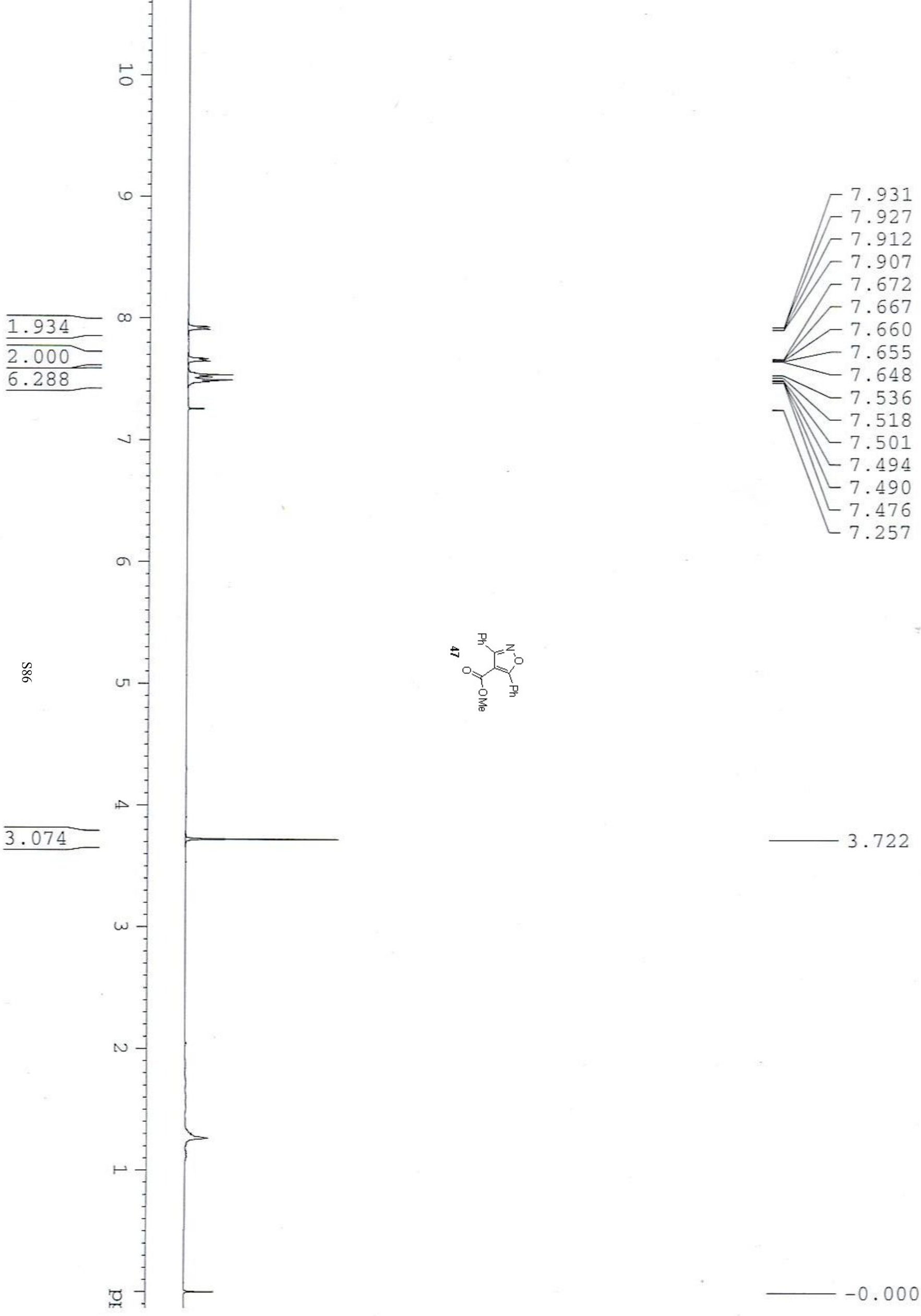
5.7088
3.0000
2.8803
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)
MeO
MeO
OMe
N
O
CH3
44
7.0623
3.9265
3.9114
2.5567

171.7381
162.3817
153.3741
139.5518
124.0235
105.8035
61.1103
57.8916
56.4017
13.1568



44

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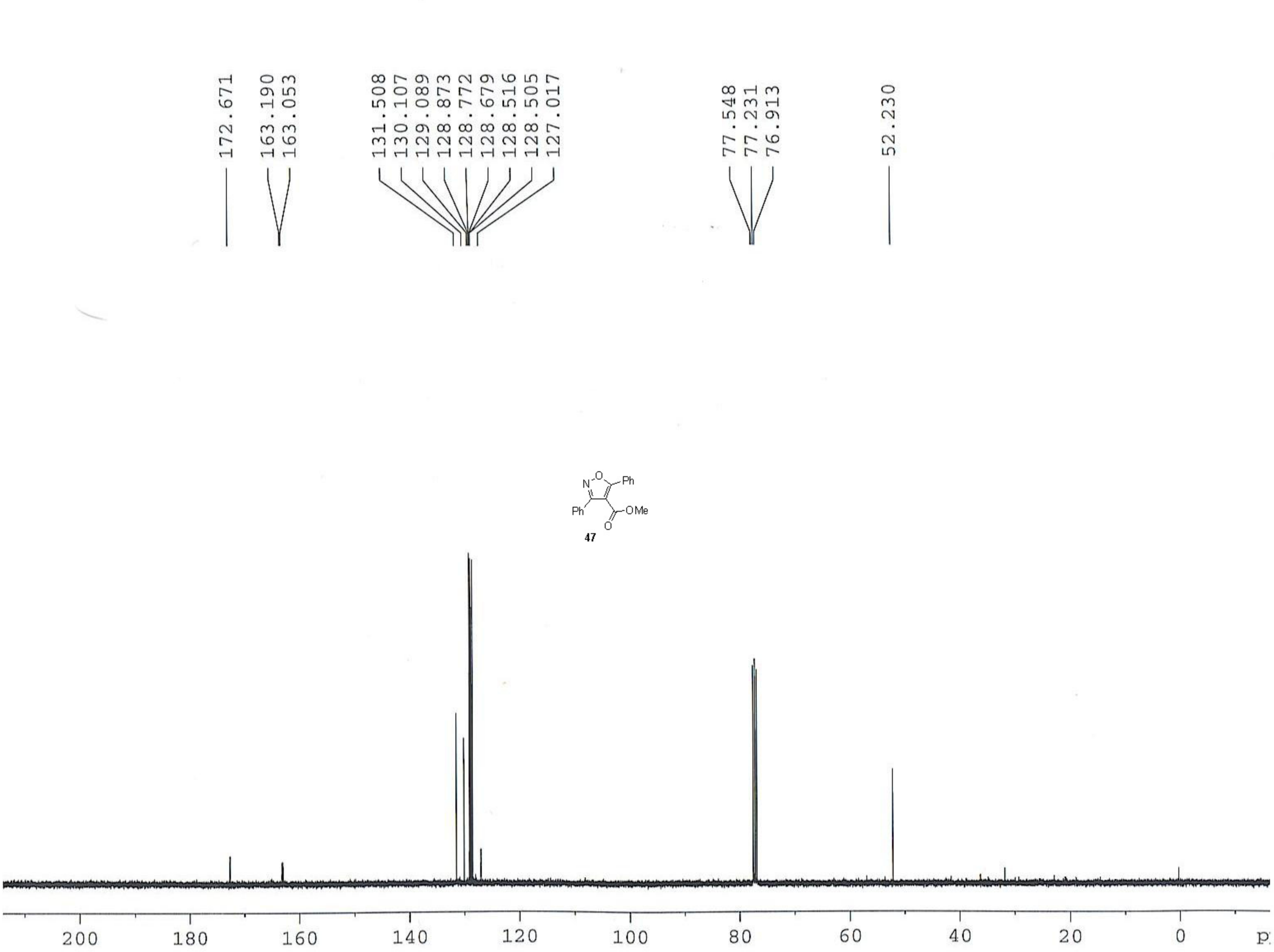
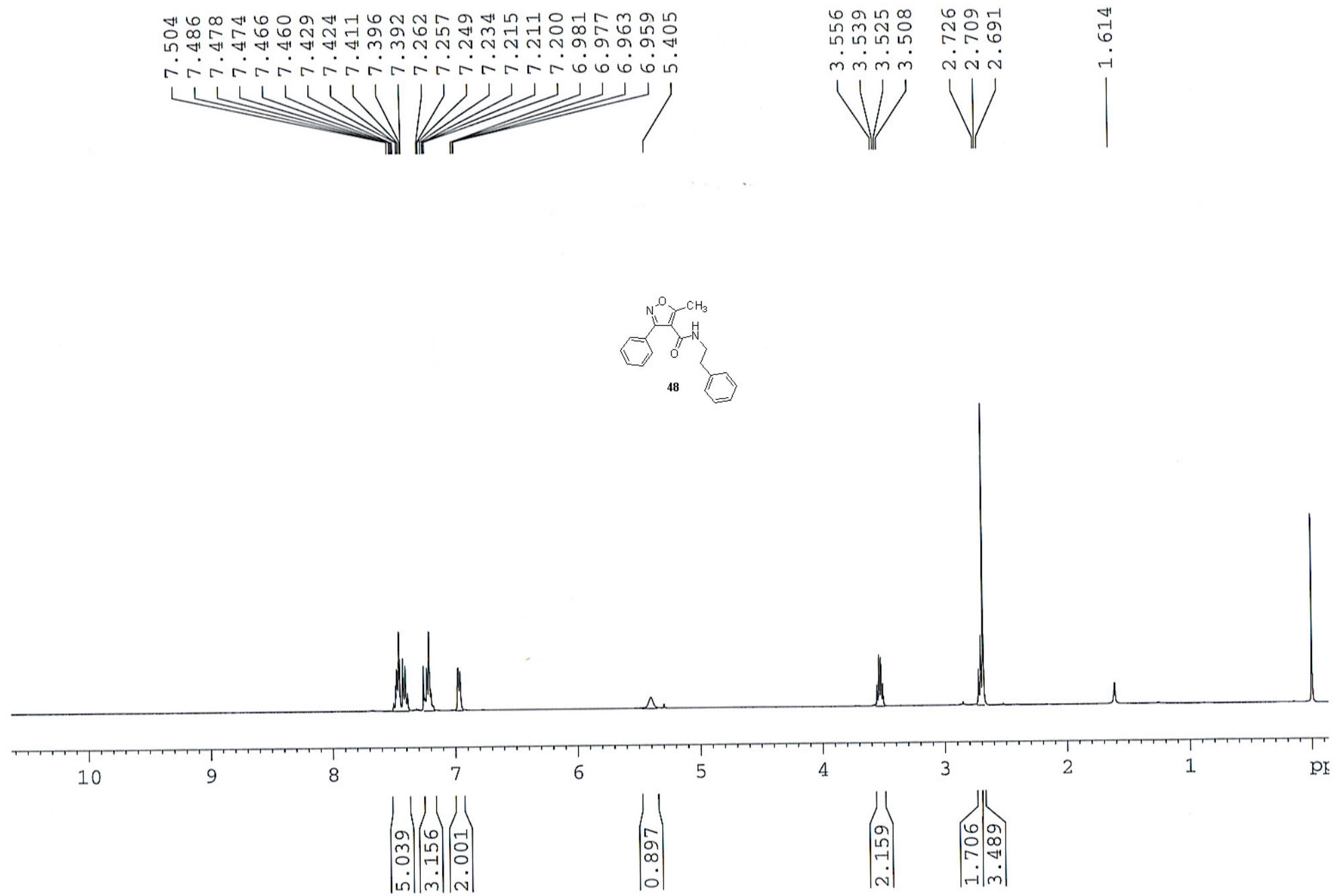
7.927
7.912
7.907
7.672
7.667
7.660
7.655
7.648
7.536
7.518
7.501
7.494
7.490
7.476
7.257
3.722
-0.000
1.934
2.000
6.288
3.074
10
9
8
7
6
5
4
3
2
1
pi
Ph
N
O
Ph
O
OMe

47

172.671
163.190
163.053
131.508
130.107
129.089
128.873
128.772
128.679
128.516
128.505
127.017
77.548
77.231
76.913
52.230

47

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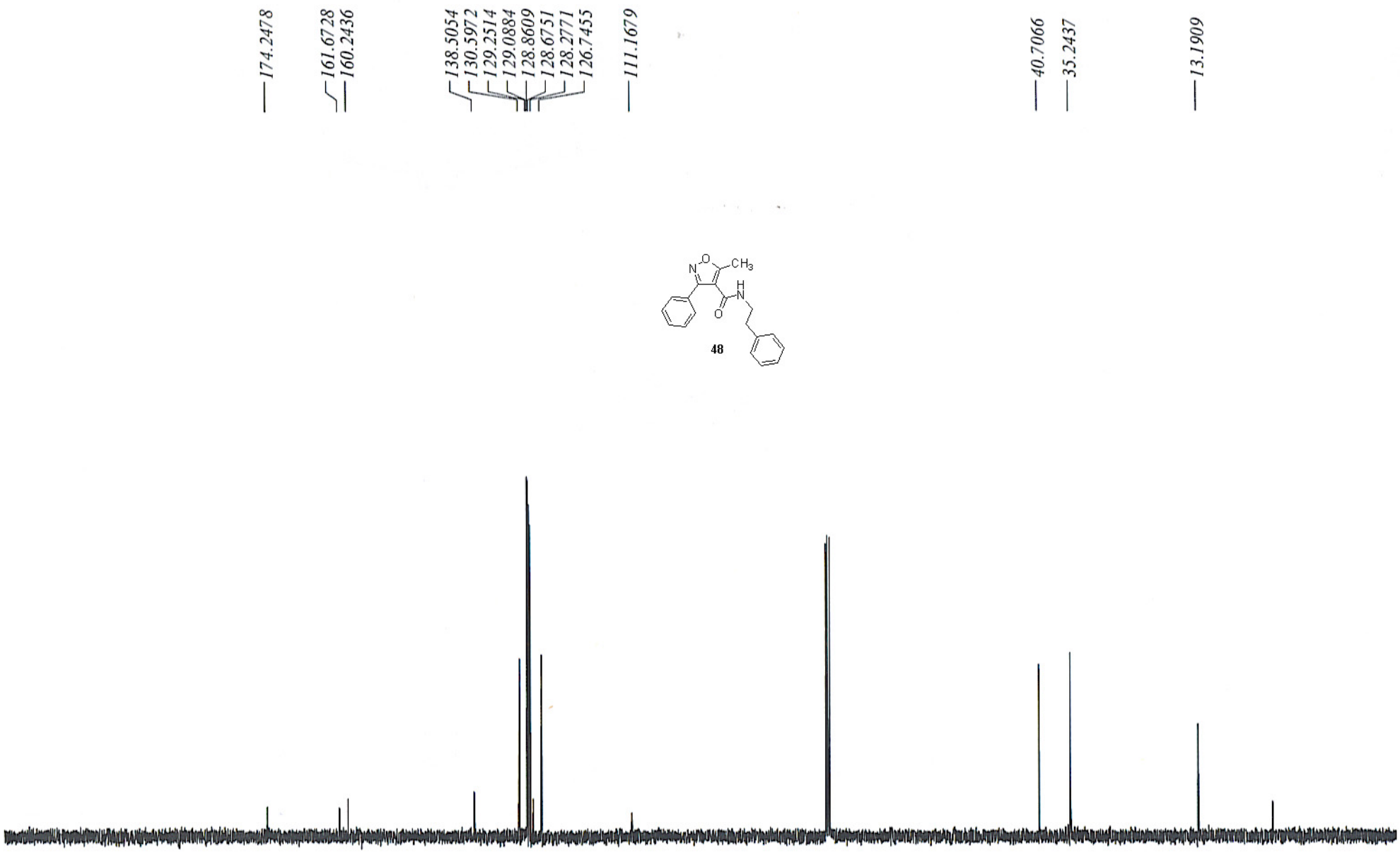
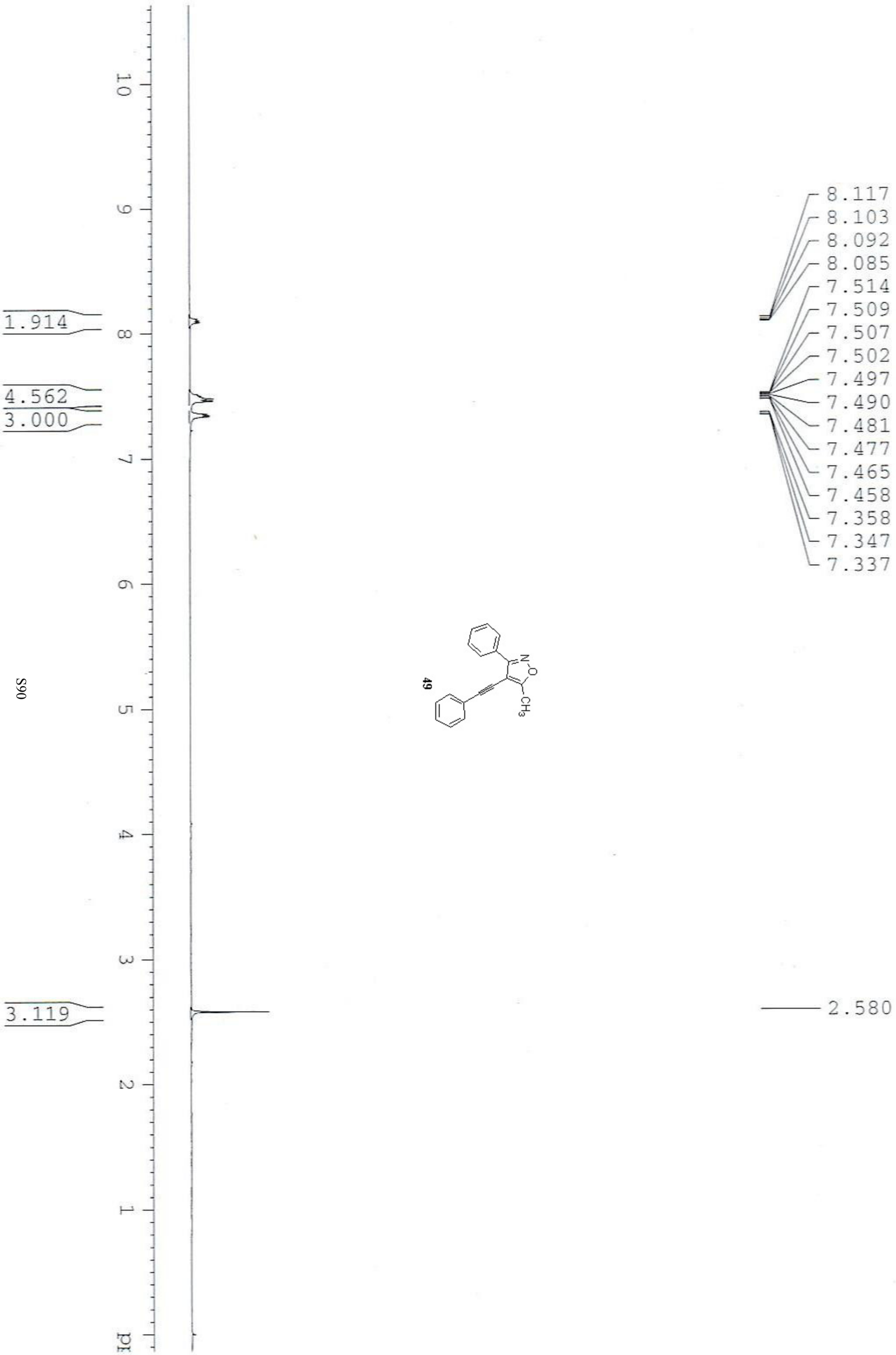
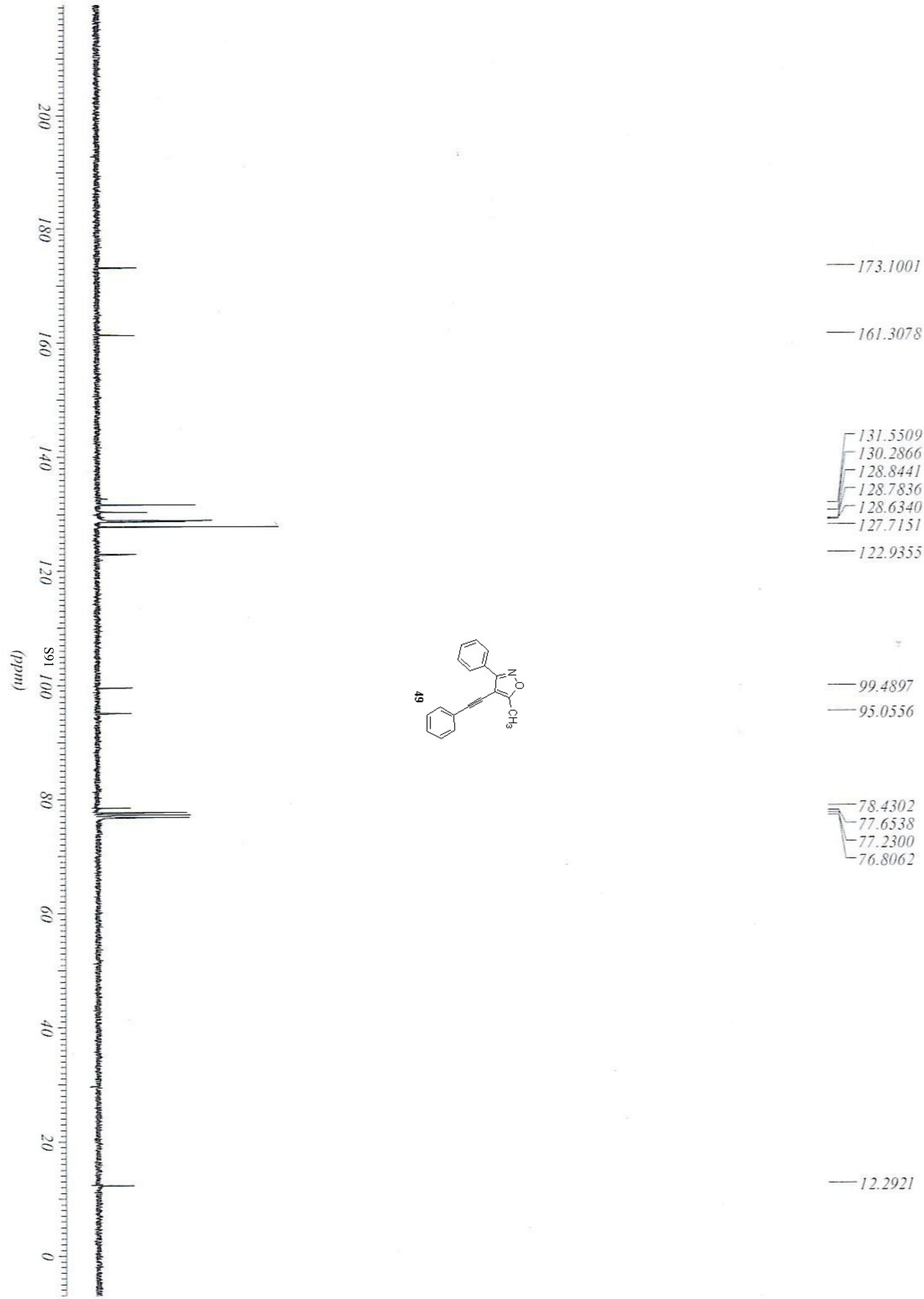
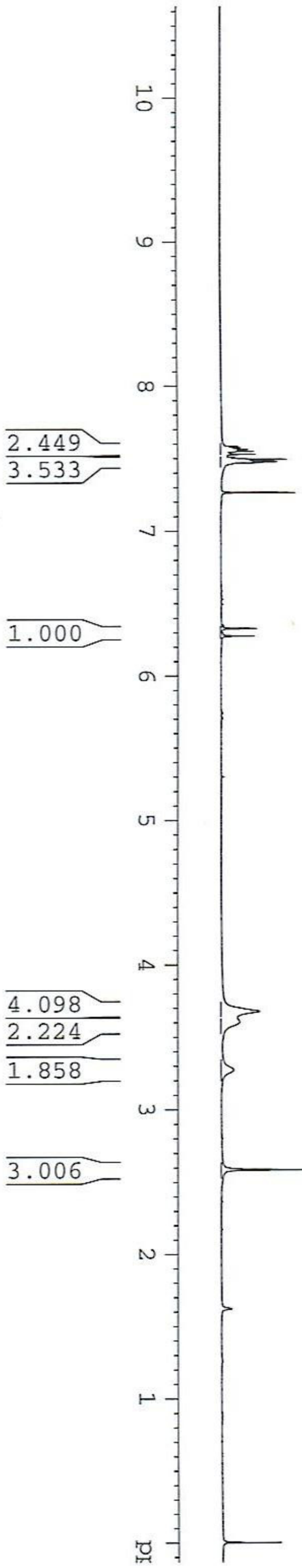
7.486
7.478
7.474
7.466
7.460
7.429
7.424
7.411
7.396
7.392
7.262
7.257
7.249
7.234
7.215
7.211
7.200
6.981
6.977
6.963
6.959
5.405
3.556
3.539
3.525
3.508
2.726
2.709
2.691
1.614
48
10
9
8
7
6
5
4
3
2
1
5.039
3.156
2.001
0.897
2.159
1.706
3.489

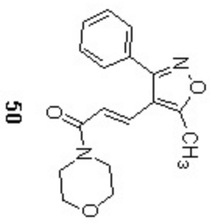

174.2478
161.6728
160.2436
138.5054
130.5972
129.2514
129.0884
128.8609
128.6751
128.2771
126.7455
111.1679
40.7066
35.2437
13.1909
CH3
N
O
H
N
O
48
200
180
160
140
120
100
80
60
40
20
0

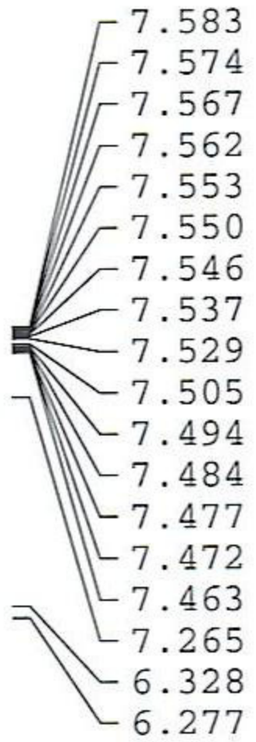

8.117
8.103
8.092
8.085
7.514
7.509
7.507
7.502
7.497
7.490
7.481
7.477
7.465
7.458
7.358
7.347
7.337
1.914
4.562
3.000
3.119
2.580
49
N
O
CH3
10
9
8
7
6
5
4
3
2
1
pt


(ppm)
0
20
40
60
80
100
120
140
160
180
200
S91
49
N
O
CH3
173.1001
161.3078
131.5509
130.2866
128.8441
128.7836
128.6340
127.7151
122.9355
99.4897
95.0556
78.4302
77.6538
77.2300
76.8062
12.2921

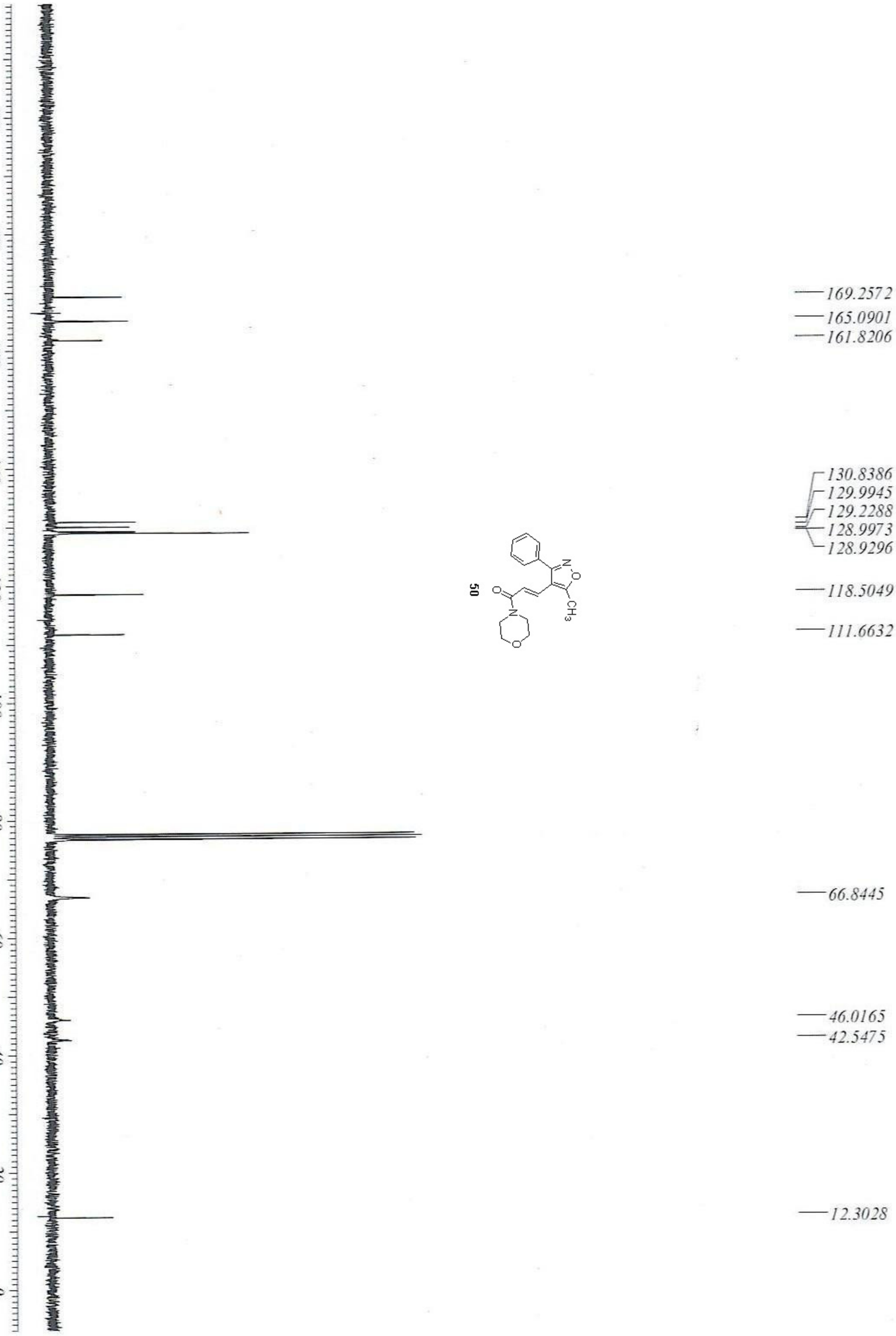

2.449
3.533
1.000
4.098
2.224
1.858
3.006
10
9
8
7
6
5
4
3
2
1
pr

50


N
O
CH3
O
N
O


7.583
7.574
7.567
7.562
7.553
7.550
7.546
7.537
7.529
7.505
7.494
7.484
7.477
7.472
7.463
7.265
6.328
6.277


3.679
3.604
3.274
2.586
0.000


(ppm)
0
20
40
60
80
100
120
140
160
180
200
169.2572
165.0901
161.8206
130.8386
129.9945
129.2288
128.9973
128.9296
118.5049
111.6632
66.8445
46.0165
42.5475
12.3028

50